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THE ELECTROENCEPHALOGRAMS OF ALLERGIC CHILDREN

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THE electroencephalogram is a recording of the action potentials of the brain, as the electrocardiogram is a recording of the action potentials of the heart. Because of the high incidence of symptoms referable to the central nervous system in allergic children, a group of children with major allergic disorders have been studied electroencephalographically and this report is on eighty-five of them. Table I summarizes the clinical material. A nonallergic control group was obtained from among the more than 400 electroencephalographic records made annually for the Pediatric Department. The allergic group consists of fifty-two males, thirty-three females, whose ages range from two to fourteen years. Approximately two-thirds of the patients are between six and twelve years of age, which coincides with the age at which major allergy is most often recognized and definitely established. No patient less than two years of age is included because of the difficulty in obtaining technically satisfactory EEG records from such young patients.

Table II shows that all major forms of allergy are represented in this group of children.* All children were sensitive to one or more types of allergen (contact, airborne and alimentary substances, infection), as shown by direct or indirect skin tests and by clinical trial. No patients with physical allergy, such as allergy to heat or cold, were encountered in the course of this study. The allergic complaints are of less than two years' duration in eighteen patients, while sixty-seven have suffered from allergic disease for more than two years. The family history was positive

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*The total number of allergic disorders exceeds eighty-five because many patients showed several allergic manifestations and appear, therefore, under more than one heading.

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TABLE I. ALLERGIC CHILDREN STUDIED ELECTROENCEPHALOGRAPHICALLY
Sex, Race, Age

1. Total Number of Allergic Children Studied.....	85
Male.....	52
Female.....	33
2. White Children	82
Colored Children	3
3. Age 2-5 Years.....	16
4. Age 6-11 Years.....	55
5. Age 12-14 Years.....	14
6. Private Patients.....	64
7. Clinic Patients.....	21
8. Twin Pairs.....	2

TABLE II. CLINICAL CONDITIONS ENCOUNTERED AMONG EIGHTY-FIVE
ALLERGIC CHILDREN

Total number of allergic disorders exceeds eighty-five because of combined allergic disorders in patients

Cutaneous Allergy.....	13
(Eczema).....	
Upper Respiratory Allergy.....	43
(Rhinitis, "Hayfever").....	
Lower Respiratory Allergy.....	56
(Asthma).....	
Gastro-Intestinal Allergy.....	3
(Nausea, Vomiting, Diarrhea).....	
Vascular Allergy.....	17
(Urticaria, Migraine).....	
Behavior Problem.....	
Associated with Allergy.....	22
Mental Deficiency.....	1
Superior Intelligence.....	11
(I.Q. above 110).....	
Convulsive Disorder.....	
Associated with Allergy.....	22

TABLE III. CLASSIFICATION OF ELECTROENCEPHALOGRAMS

Total exceeds eighty-five because of combined abnormalities in certain patients

1. Regular Rhythmic-Repetitive Electro-Activity, Stable to Overventilation.....	5
2. "Within Normal Limits," Stable to Overventilation.....	9
3. "Within Normal Limits," Unstable to Overventilation.....	6
4. Irregular, No Further Changes to Overventilation.....	6
5. Irregular, With Further Changes to Overventilation.....	10
6. Dysrhythmia, Predominantly Frontal.....	10
7. Dysrhythmia, Predominantly Occipital.....	42
8. Spike-and-Waves.....	7
9. Focal Disturbance.....	3
10. "Low Voltage" Record.....	1

for allergy of the same or different type in sixty-four patients, negative in eighteen and unknown in three. A history of allergic disorder existed equally often among the paternal as among the maternal relatives.

Accessory diagnoses which may be of interest electroencephalographically are shown also in Table II. These include convulsive disorders, behavior problems, superior intelligence and mental deficiency. Twenty-two patients had a convulsive disorder for which no immediate cause could be demonstrated. Twenty-two patients with a convulsive disorder (petit and grand mal) is a high number in a series of eighty-five allergic children, when one considers the incidence of convulsive disorders usually observed among the general allergic population. However, we have made it our practice to test for allergy those patients with cryptogenic convulsions whose personal or family history suggested the possibility of an allergic disorder. Three patients had a history of a single convulsion of unknown origin in early childhood; two, a history of convulsions with fever only.

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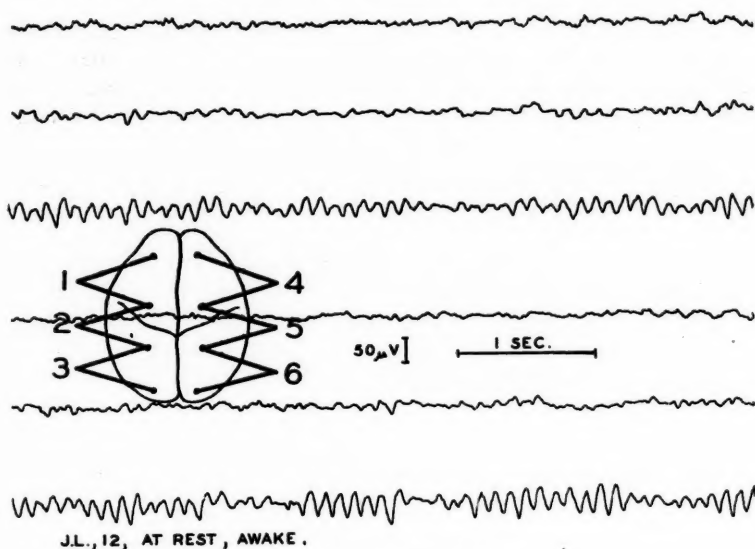


Fig. 1. Normal electroencephalogram.

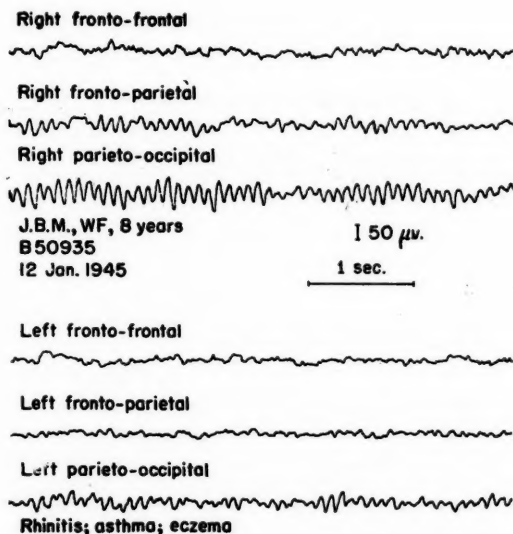


Fig. 2. Electroencephalogram within normal limits in eight-year-old girl with asthma, eczema, and allergic rhinitis.

The electroencephalograms were obtained with the Grass electroencephalograph, six monopolar or six dipolar tracings being recorded simultaneously for about twenty minutes. Each patient was asked to over-

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ventilate for five minutes. The records were classified into categories as shown in Table III. On this basis, twenty electroencephalograms fall within groups 1 to 3, or normal, as illustrated in Figure 1, while sixty-five records show definite abnormalities of varying degree. Fifty-two

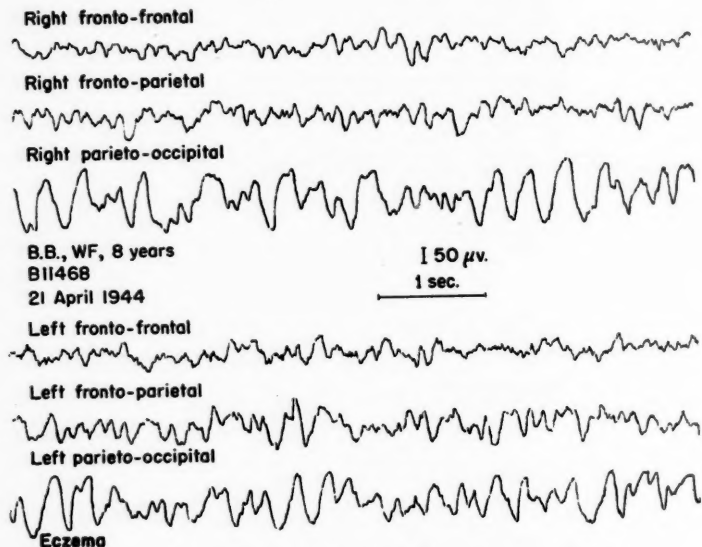


Fig. 3. Severe generalized cerebral dysrhythmia more pronounced in occipital region in an eight-year-old girl with eczema.

electroencephalograms showed cerebral dysrhythmia, of which ten were predominantly frontal, forty-two predominantly occipital, in type. Representative records from patients showing predominantly occipital dysrhythmia are shown in Figures 2 through 5.

Because of the combination of several allergic disorders in any one patient, unavoidable overlapping of diagnoses occurs when one expresses the incidence of any EEG finding in relation to a single allergic disorder. For this reason, the incidence of occipital dysrhythmia is considered for the group as a whole. Occipital dysrhythmia was present in forty-two of our eighty-five patients, essentially one-half of the entire group. Since twenty-one patients, or one-quarter of the group, had normal records, the forty-two occipital dysrhythmias account for two-thirds of the abnormal records; the remaining third comprises all other types of abnormalities. The occipital dysrhythmia was not confined to any one allergic condition, but appeared in approximately one-half of all patients with all types of allergic disease. There seemed to be no difference between patients with one allergic disorder compared to those with multiple allergic manifestations. If one considers separately the sixty-three children with allergy without convulsions, twenty-nine patients (45 per cent) show cerebral

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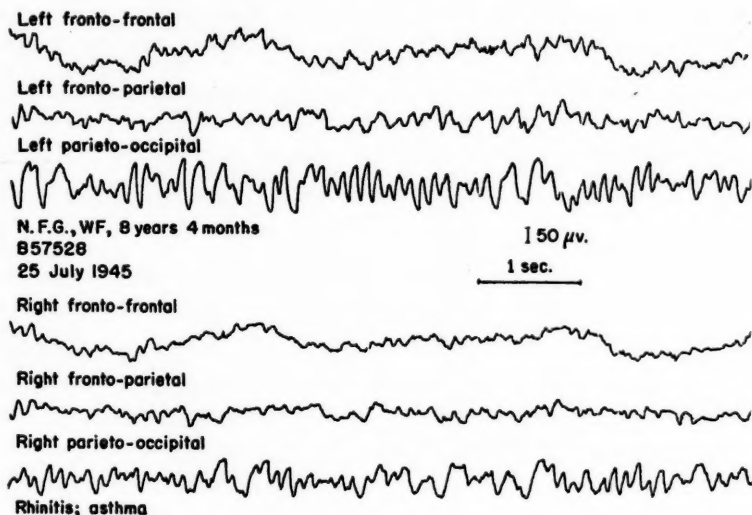


Fig. 4. Generalized predominantly occipital dysrhythmia in eight-year-old girl with allergic rhinitis and asthma.

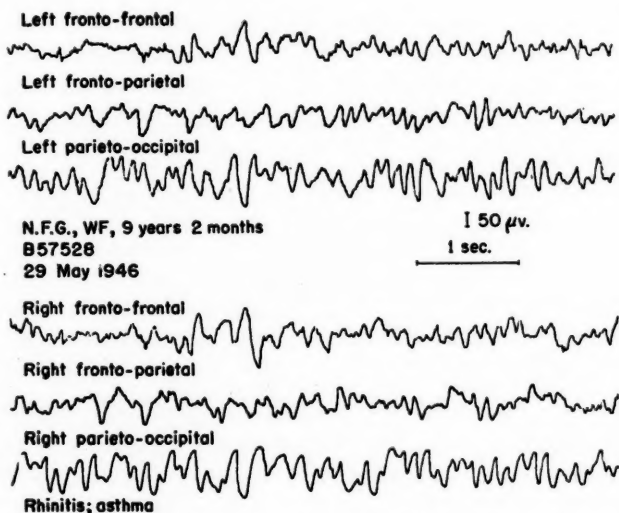


Fig. 5. Follow-up electroencephalogram of patient in Figure 4, ten months after desensitization, with marked improvement in asthma and allergic rhinitis, no change in electroencephalogram.

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dysrhythmia, and in twenty-six of these the predominant abnormality is consistently occipital in location, as shown in Figure 6. Of the remaining twenty-two children who had a convulsive disorder in addition to allergic disease, occipital dysrhythmia was present in thirteen. Frontal

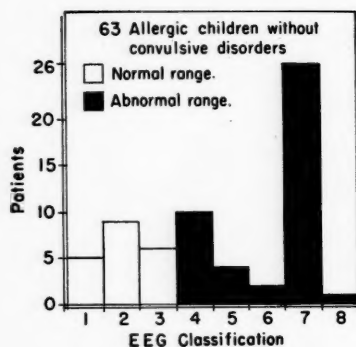


Fig. 6. Distribution of electroencephalograms in allergic children without convulsive disorder. See Table III for classification of electroencephalogram.

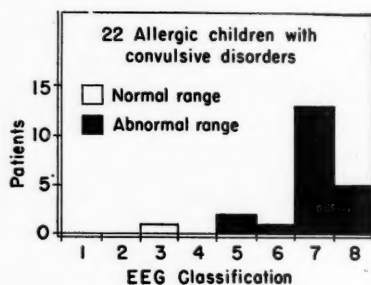


Fig. 7. Distribution of electroencephalograms in allergic children with associated convulsive disorder. See Table III.

dysrhythmia occurred once, while spike and wave pattern appeared in five, or one-quarter of the records. The over-all percentage of predominantly occipital dysrhythmia was 59 per cent in the convulsive group (Fig. 7). That this figure is slightly higher than in the children without convulsive disorders is not surprising when one considers the regularity with which abnormal EEG's are encountered in convulsive disorders. The point to be emphasized is the high incidence of abnormal records in those children with allergy alone which previously has not been thought to be associated with any one characteristic EEG pattern.

We could find no relationship between EEG patterns and the sensitivity to different types of allergens. Those patients with purely seasonal allergy had as high an incidence of occipital dysrhythmia and of other types of abnormalities as did the other patients.

The incidence of occipital dysrhythmia among patients with allergy of less than two years' duration was 30 per cent. Sixty-seven patients gave a history of allergy of more than two years' duration, and in these the occipital dysrhythmia had increased to 55 per cent. As occipital dysrhythmia thus might be related to the duration of the allergy, further confirmation was sought from a slightly different point of view of noting the percentage of occipital dysrhythmia in increasing age periods. Occipital dysrhythmia increases sharply up to 72 per cent in the six to seven-year-olds and remains high (63 per cent) through the ninth year. A decrease in occipital dysrhythmia occurs after the tenth year (Fig. 8).

An analysis of the electroencephalogram in relation to the type of

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family history shows that of sixty-seven patients with a positive family history of allergy, 45 per cent had an occipital type dysrhythmia. Among the remaining patients with a negative family history, the occipital dysrhythmia occurred only half as frequently, namely, in 22 per cent of the

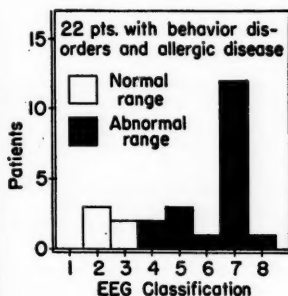
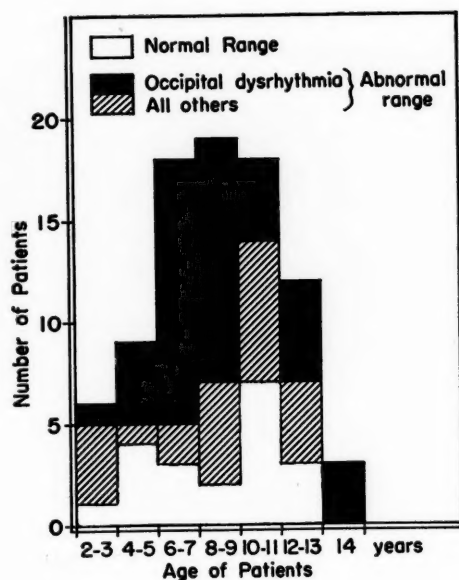


Fig. 8. (left) Distribution of electroencephalographic changes encountered in allergic children in relation to age of patients. See Table III.

Fig. 9. (above) Distribution of electroencephalograms in patients with behavior disorder associated with allergic disease. See Table III.

patients. Normal records or records within normal limits were found with approximately equal frequency in both groups (26 per cent and 22 per cent).

After a period of three months to four years (in a few instances up to six years), one or more additional electroencephalograms were obtained on thirty-six of the patients. The records were unchanged in twenty-five and showed improvement in eleven. All patients whose electroencephalogram was improved, reported improvement of their allergic symptoms. On the other hand, clinical improvement was often found without significant change of the electroencephalogram. The type of electroencephalographic changes are unrelated to the type of allergy, the duration of the disease, or a positive or negative family history.

In view of the similarity of the EEG abnormality encountered in these patients with those seen in patients with behavior disorders (Fig. 9), or convulsive disorders or their equivalent, the use of Dilantin sodium suggests itself as a possible rational therapeutic agent in the children with

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occipital dysrhythmia. That the drug is useful in controlling asthma, has been reported by Shulman.⁶ His patients were selected on purely clinical grounds and apparently without electroencephalographic correlation. We, too, have used Dilantin in a number of our allergic patients but time has

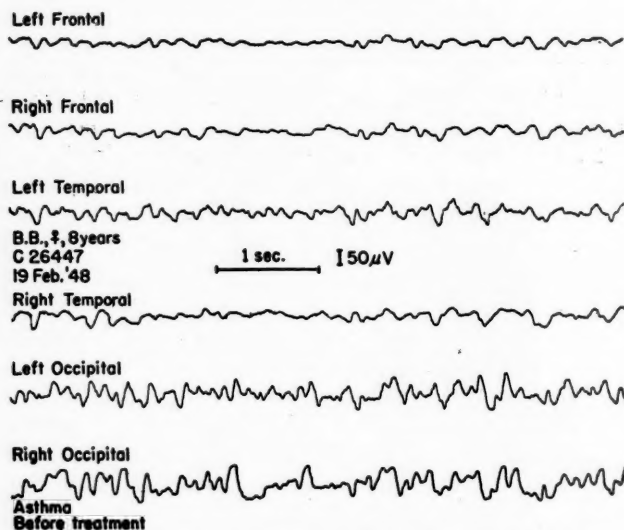


Fig. 10. Occipital dysrhythmia in an eight-year-old girl with asthma. Before Benadryl.

been too short to permit an appraisal. However, we do not feel justified, at present, in substituting Dilantin for the usual antiallergic drugs and desensitization in the routine treatment of allergic children. The effect of Benadryl on the electroencephalogram has been studied in a few patients. This medication for several days may be followed by improvement in the EEG as shown in Figures 10 and 11. However, thirty minutes after administration of a single 25-50 mg. dose of Benadryl, no change has been detected in the EEG in several patients. None of the children to whom the drug was given, who had EEG studies, experienced any central nervous system effect. It has not been possible for us to study the EEG of any who had reactions such as somnolence or excitement.

DISCUSSION

We have presented the results of an electroencephalographic study of eighty-five allergic children. The outstanding feature is that occipital dysrhythmia occurs in half of the patients. This is a far higher figure than one would expect to encounter in a similar group of so-called "normal" children.^{1,3,4,7} As will be recalled, we have as basis for this statement nearly 3,000 records from the Pediatric Department, on children of all ages, many of whom have no disease, and among these

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records there is no similar preponderance of occipital dysrhythmia. The combination of allergy, convulsions, and behavior problems does not significantly increase the incidence of occipital dysrhythmia over that seen in allergy alone.

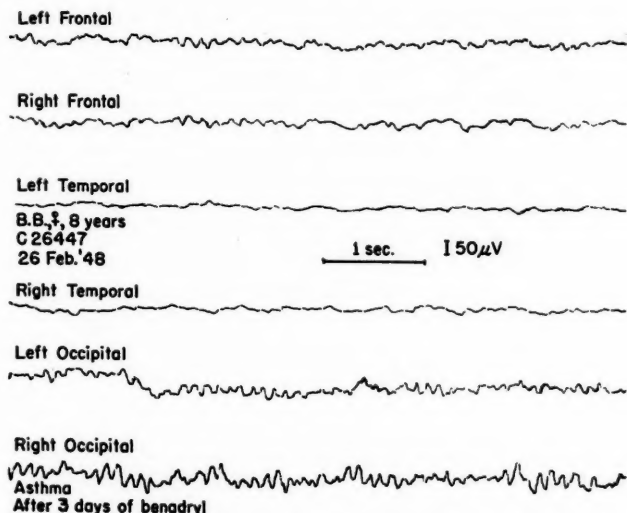


Fig. 11. Electroencephalogram in the eight-year-old girl of Figure 10, three days after instituting medication with Benadryl.

There are two factors which do appear to have a definite correlation with a high incidence of occipital dysrhythmia. The first, is the presence of a positive family history of allergy, irrespective of whether the allergy is of the same or different type, whether the inheritance is from the maternal or paternal line. A positive family history was associated with occipital dysrhythmia twice as frequently as was a negative family history. This is similar to the high incidence of abnormal electroencephalograms in the nonepileptic relatives of epileptics.⁵

The second factor seems to be the duration of allergy. The longer the duration, the higher is the percentage of patients who show changes in the occipital pattern. The significance of these observations is not clear at present, since further attempts to correlate the facts were inconclusive. The incidence of abnormalities of the EEG tends to decrease with increasing age. This is similar to the observation among patients with dysrhythmia due to manifest convulsive disorders (e.g., Gibbs et al²).

At present, we can offer no explanation why abnormal electroencephalograms should occur so frequently among allergic children. We also do not know why the parieto-occipital regions should be particularly, sometimes almost selectively, affected. The parieto-occipital electroactivity is the

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most stable and repetitive of the regional patterns in adult life and under normal circumstances. In children, and certainly in allergic children, the occipital areas are the most vulnerable electroencephalographically.

The occurrence of abnormal cerebral potential may offer an explanation for the clinical observation that allergic children so frequently present special personality problems. Usually, emotional frustrations and physical demands, like dietary deprivations, restriction of activities, the "itch" and the "stopped-up nose" have been declared sufficient to account for the heightened irritability, the surliness and other psychological difficulties of the allergic child. It seems that a great deal of such behavior might be explained by a central nervous system which does not function smoothly and efficiently. At this point, it remains a fruitless speculation whether the same noxa is responsible for both the clinical allergy and the dysrhythmia, or whether one or the other is causally interdependent.

CONCLUSIONS

1. Electroencephalograms are abnormal in a high percentage of allergic children, irrespective of whether allergy is complicated by behavior problems or convulsive disorder or a history of convulsive disorder.
2. Irregularity is predominantly occipital dysrhythmia in practically one-half of patients with all types of allergic disease.
3. Incidence of occipital dysrhythmia seems to increase with the duration of allergic symptoms.
4. Occipital dysrhythmia appears to occur twice as frequently in patients with a positive family history of allergy as in those with a negative family history.
5. Since occipital dysrhythmia and other types of abnormalities were present in essentially the same proportion in patients with allergy complicated by behavior problems and convulsions, as in those children with allergy only, one may assume that, in these patients, it is not the behavior problem or convulsions which are always responsible for the abnormality, but that the allergy also may be expressed in an abnormal electroencephalogram.

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EXPERIMENTAL STUDIES ON ACUTE DISSEMINATED ENCEPHALOMYELITIS IN THE RHESUS MONKEY

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PREVIOUS studies from this laboratory and by Morgan at Johns Hopkins have demonstrated that the acute disseminated encephalomyelitis, first produced by Rivers and Schwentker by injection of brain emulsions, could be regularly and rapidly induced by incorporation of brain or spinal cord tissue with certain adjuvants, paraffin oil, aquaphor (a lanolin-like substance), and killed tubercle bacilli; these adjuvants have been shown by Freund to give enhanced antibody formation to a variety of other antigens. The acute disseminated encephalomyelitis produced in the monkey resembles acute disseminated encephalomyelitis and multiple sclerosis in man in many respects.

The mechanism hypothesized to explain these phenomena was that antibodies were produced to the injected brain tissue which passed into the circulation and through the capillaries of the brain and spinal cord to react with antigen in the animal's central nervous tissues to produce the lesions, and the perivascular distribution of the lesions was considered as strong evidence in support of this concept.

Subsequent studies have been directed toward further elucidating the mechanism by which this experimental disease is induced and toward identification and purification of the inciting substance in brain tissue. The dead tubercle bacilli have been found essential for the rapid production of the disease with but a few injections, and examination of the local inoculation sites showed that the large numbers of epithelioid cells, which characterized the local lesions when tubercle bacilli were used, were absent if the tubercle bacilli were omitted. That the action of the tubercle bacilli takes place at the inoculation site and is not due to a systemic action of the tubercle bacilli was indicated by the negative results obtained on injecting emulsions of brain, paraffin oil and aquaphor into one arm and tubercle bacilli, paraffin oil and aquaphor into the other arm. Encephalomyelitis could be produced in monkeys by emulsions with adjuvants of adult monkey, rabbit, human and chicken brain, but not with adult frog or fish brain or with fetal rabbit brain. Injection of brain and spinal cord emulsions from rabbits of varying ages after birth, during the period when myelination is occurring, showed that the antigen appears in spinal cord at an earlier stage than in brain, suggesting that its appearance may be correlated with the laying down of myelin. Efforts to produce the disease by passive transfer with the serum of monkeys showing encephalomyelitis have been

(Continued on Page 130)

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PSYCHOSOMATIC ASPECTS OF HAY FEVER AND ASTHMA PRIOR TO 1900

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EVEN in their relatively primitive therapy, our medical ancestors not only seem to have recognized syndromes of hypersensitivity but also to have stressed a relationship between the psyche and allergic diseases. The same centers of controversy also persist today. Certain aspects of the development of psychiatric theory for these disorders up to the latter part of the last century will therefore be briefly outlined.

To begin with, Hippocrates⁸ had an understanding of the role of both emotional and physical factors in disease. The former were classified as hysteria and hypochondria. "Fears, shame, pleasure, passion . . ." he says, "to each of these the appropriate member of the body responds by its actions. Instances are sweats, palpitations of the heart . . ."

Hippocrates further recognized, as did many of his followers, what we today call food allergy. This is illustrated in Figure 1 by a translation of a direct quotation.

THE "ROSE FEVER SYNDROME" OF THE SEVENTEENTH CENTURY

The early history of pollen hay fever is complicated by the fact that the discussions on this subject found in the 17th and 18th Centuries cover at least two distinct clinical entities accidentally connected with the blooming of the rose. On the one hand, unusual and bizarre clinical reactions to the rose were described, where the patient was affected either by the sight or by the odor of roses. These peculiar reactions were general in nature, e.g., fainting, and hardly connected explicitly with allergic rhinitis as we know it today. On the other hand, local nasal and ocular symptoms occurred during the time when the roses were in bloom. These symptoms were similar to hay fever as we know it today. They were not connected with the presence of roses, but usually with the time of their blooming.

Let us quote some examples to be found in the writings of this time. Binnigerus² (1673), in an article entitled, "Fragrant Objects Which Purge the Body," states:

"L. B., a student of medicine, now a physician, has an extraordinarily constituted olfactory organ. Odors of objects of a pleasant or agreeable

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Wherefore it appears to me necessary to every physician to be skilled in nature, and strive to know, if he would wish to perform his duties, what man is in relation to the articles of food and drink, and to his other occupations, and what are the effects of each of them to every one. And it is not enough to know simply that cheese is a bad article of food, as disagreeing with whoever eats of it to satiety, but what sort of disturbance it creates, and wherefore, and with what principle in man it disagrees; for there are many other articles of food and drink naturally bad which affect man in a different manner. Thus, to illustrate my meaning by an example, undiluted wine drunk in large quantity renders a man feeble; and everybody seeing this knows that such is the power of wine, and the cause thereof; and we know, moreover, on what parts of a man's body it principally exerts its action; and I wish the same certainty to appear in other cases. For cheese (since we used it as an example) does not prove equally injurious to all men, for there are some who can take it to satiety without being hurt by it in the least, but, on the contrary, it is wonderful what strength it imparts to those it agrees with; but there are some who do not bear it well, their constitutions are different, and they differ in this respect, that what in their body is incompatible with cheese, is roused and put in commotion by such a thing; and those in whose bodies such a humor happens to prevail in greater quantity and

Fig. 1. Hippocrates. *Translations of the Aphorisms*. Page 143. By Francis Adams. London: William Wood, 1886.

nature vanish in a short time; whereas very fetid odors remain with him for a long time so that they could not be made to disappear for many hours. An honorable lady . . . the wife of an eminent personage . . . suffered from coryza at the time of the blooming of the roses . . ."

Binningerus' first patient, L. B., reacted to odors in a peculiar way. However, Binningerus classified L. B. and the "honorable lady who suffered from a coryza at the time of the blooming of the roses," in the same paragraph. But evidently these two syndromes are not connected, the first reaction being a disorder of olfaction, whereas the second is characteristically an allergic rhinitis.

Ledelius¹⁰ (1683) points out that a merchant of "melancholic temperament" reacted to the smell of roses with a fairly typical syndrome of hay fever. However, the intense emotional attitude toward the odor of roses, apparently fairly common at that time, is brought out by Hunnerwolf⁹ who, in 1686, went so far as to state:

"There are some to whom the odor of the rose is so harmful that at times it causes sickness and at other times it accelerates death. Examples of sudden death resulting from this cause are found here and there throughout the annals of medicine. It is remarkable that from this same cause headaches, toothaches, sneezing, smothering, fainting and eruptions of the blood are directly traceable. I know a man who suffered a severe

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nasal catarrh as often as he entered a rose garden when it was in bloom, or whenever he smelled a rose bud."

Most interesting of all is the relationship of the symbolism of the rose to the symptoms produced by it. Valerianus¹⁷ published in 1678 a pertinent passage:

"There was a famous leader of soldiers who was so opposed to pleasures that he would swoon as soon as he perceived the fragrance of roses as though this were proof that valor, however manly, becomes enervated by allurements. This story is also handed down by Aristotle and gave occasion for a silly hieroglyphic. If an artist wished to depict stern Hannibal as being effeminate or as doubting, or yielding at Capua, he would give him a shield with the sign of a beetle and around the edge of the shield would entwine wreaths of roses. There are very many persons who cannot endure the exhalation of roses and among these are even rather great men. For when I was at Rome I saw Oliver Caraffa, a Cardinal of great celebrity, who was forced to withdraw every year at the time the roses were in bloom and to shut himself up within the gardens he had at the Quirinal. Guards were placed at the gates so that no one coming either to greet him or for the sake of friendship would bring a rose along. Among the Roman nobility there was Peter Melinus, remarkable for his ability, erudition and family position, who was greatly affected by the smell of roses."

It is obvious that the fainting attack produced by the fragrance of roses could not be caused solely by an immunologic reaction to an odor. The sight of and the fragrance of roses must have had, in addition, some other significance. The fact that roses were used to ornament the shield of a man who was considered to be effeminate or vacillating is a direct and still valid connection of the rose with effeminateness. It is most suggestive that the emotional reaction to the rose of some of the individuals under discussion at that period of time was connected with a symbolic representation of femininity, weakness and indecision. The fact that the Cardinal, referred to in the citation of Valerianus, was comfortable in his gardens with other flowers, provided that no roses were present, is indicative of the special significance of the rose—and it seems unlikely that this significance is only immunologic (if at all) in character. Unquestionably the answer must be sought in the Cardinal's attitude toward the rose as a symbol.*

*It may be of interest to those who follow symbolism in psychoanalytic psychology, to connect further the act of giving someone "the rose" in the 17th Century with giving someone "the razz" in the 20th Century. It is well known, of course, that to give somebody the "razz" is to give him the "raspberry." The raspberry is closely related to the rose and, in fact, belongs to the same family. Is there any cultural process by which giving "the rose" in the 17th Century has led to giving the "razz" in the 20th Century? Although the matter may be one of coincidence, it is worthy of further exploration.

We are not taking up the possible other symbolisms of the flowering rose, aside from the fact that it definitely represented femininity. There are, of course, other connotations.

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More clearly on an allergic basis is the observation by De Rebecque⁴ who stated in 1691:

"I have thought it useful to relate the effects which roses have on me. From my thirteenth year at the rose-blooming time, each year, I am attacked by a running catarrh in which for many days a thin and sharp fluid flows from the nostrils, and the eyes are also affected so that tears are caused to flow. This state lasts as long as the rose season. When the rose season is over this condition stops of itself. In the first years I thought this was due not to roses but to the warm summer, but after more careful consideration of the affair I have found out that it is due solely to the roses."

The general attitude toward roses in the period seems to have weighted this author's opinion so that he ascribed his symptoms directly to roses, although he quite clearly connected his symptoms to the blooming time of roses. His symptoms were, in all likelihood, those of pollen hay fever.

At the beginning of the 19th Century, then, there was a confused picture of the special effects of roses. This confusion began to clarify itself when Bostock reported in London a case of periodic infection of the eyes and chest and described his own symptoms as he had observed them over a period of thirty-eight years. In a second paper appearing in 1828, the term, "hay fever" appears. It had been associated by the public in general with new hay: Elliotson⁵ was the first to emphasize in the medical literature that the pollen of flowers was responsible, although many people before him who had been interested in the syndrome also felt that the pollens were responsible. From this time on, the role which pollen and pollen allergens played in producing seasonal hay fever is quite clear. Not so clear, however, is the type of paroxysmal sneezing and hay fever-like symptoms which were also observed in the absence of pollen. The significance of roses rapidly diminished. Thus, in a questionnaire which was sent out by George M. Beard,¹ a New York neurologist, in 1879, we find among 500 replies only five who believed that roses caused the paroxysms. Anxiety, on the other hand, was chosen in sixteen of the 500.

Dust (in-door and out-door).....	104
Hay (dried or fresh).....	48
Over-exertion	38
Gaslight	36
Flowers	31
Roses	5
Dampness	29
Foul air	29
Indigestion	29
Smoke	27
Chills	25
Anxiety	16

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In other words, in the late 19th Century there were three times as many who believed, as far as this questionnaire is concerned, that anxiety rather than roses was the cause of the hay fever-like symptoms. Beard laid particular stress on the following facts: (1) that the temperament of hay fever patients was predominantly nervous; (2) that nervous symptoms, that is, sick headaches, backaches, frequently skin diseases, et cetera, were often present in hay fever. He states:

"Headaches of nearly all kinds, backaches, neuralgia, sleeplessness, and it is now beginning to be recognized, certain skin diseases such as prurigo and, in the opinion of some, certain varieties of eczema, are largely nervous affections. That is, the nervous element predominates in them." He concludes, "Hay fever is essentially a neurosis—that is, a functional disease of the nervous system."

Emphasis on the neurotic element in hay fever appears in *Hay Fever and Paroxysmal Sneezing*, by Morrell Mackenzie,¹¹ which was published in 1887. Among his numerous references which show surprising insight is the following:

"It has long been noticed that attacks of prolonged sneezing are most apt to occur in persons of nervous temperament. . . . It is also well known that in states of great emotional sensibility sneezing is apt to occur.

"That sneezing often depends on the morbid excitability of a centre is shown by the fact that a person who is subject to such paroxysms will often remain for many hours free from an attack when his mind is occupied, whilst when unemployed the attacks may be frequent.

"There are certain supposed fallacies in the pollen theory which must be referred to. Thus, a case is mentioned by Dr. Walshe, in which a patient retained the symptoms of hay fever during a passage across the Atlantic, and another has been reported by Dr. Abbott Smith in which the disease came on at a distance of nine miles from land.

"However, these examples are not unequivocal since allergens of many kinds exist on board ship.

"The phenomena of hay asthma, though their origin may be different, are, like those of asthma, in general of a neurotic type and it would appear that in some cases hay fever has been of what Dr. Carpenter calls an ideo-motor character."

Dr. Mackenzie describes the case of a "young lady who suffered so acutely from hay fever that she always remained in London till after the hay was got in. On one occasion, however, after a visit to the Royal Academy, where she had been much struck by a highly realistic painting of a hay field by Mr. Vicat Cole, she had a severe attack of her familiar complaint."

The present state of paroxysmal attacks of sneezing, nasal obstruction, rhinorrhea, usually of short duration, if not accompanied by any of the symptoms usually found when an infection

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is present, and not confined to any particular season, is considered by some to be allergic. However, the large variety of names which this type of vasomotor rhinitis has had applied to it is of significance and illustrates how ill-defined this syndrome is:¹⁶

1. Vasomotor rhinitis
2. Perennial non-seasonal rhinitis
3. Perennial non-seasonal allergic rhinitis
4. Paroxysmal rhinitis
5. Nervous rhinitis
6. Hyperesthetic rhinitis
7. Intrinsic rhinitis
8. Allergic coryza
9. Spasmodic coryza
10. Paroxysmal rhinorrhea
11. Perennial hay fever
12. Hydroa nasalis
13. Allergic rhinopathy

We have, indeed, a difficult subject to deal with. In view of its history and its modern clinical and laboratory implication, it appears very likely that a large fraction of these cases have an emotional content, the psychodynamics of which still remain to be explored.

ASTHMA

Both Hippocrates and Aretaeus mention asthmatic symptoms. Hippocrates recognized that *anger* and *hostility* influenced the asthmatic paroxysm. In the 7th Century, Aeginita stated that, "*Those who breathe thick without fever, like those who run fast, are said to be asthmatic; that is, to pant for breath, and for being obliged to keep the chest erect for fear of being suffocated. They are called orthopneics.*"

The concept of nervous or spasmodic asthma characterized by attacks of paroxysmal panting without infection, as described above, was recognized by J. B. Van Helmont¹⁸ (1577-1644), who pointed out and emphasized the spasmodic element in asthma in its sudden onset and the way in which it occurred in attacks like epilepsy.

Up to the 17th Century the opinions of Galen and other Greek physicians were quoted and had remained essentially unchanged for more than a thousand years. At this time, however, numerous publications appeared giving detailed descriptions of the symptoms, causes and cures for asthma, dyspnea, "the fits," amongst other names for this syndrome. Among these physicians there were a few who sensed that in some cases of spasmodic asthma the initiation of the attacks and their subsequent relief *could not be simply traced to any known physical or organic cause.*

Thomas Willis¹⁹ was an early pioneer who expressed the idea that asthmatic attacks might be attributed to emotional disturbance.

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In 1684 he states in his book, *On an Asthma*, that, "... hindering or perverting the work of breathing brings on the disease ... for," he goes on, "the animal spirits destined to the function of breathing, if at any time they are much molested and constrained into

As for dry Athma's ; They may proceed from a preternatural form of the Back and Breast, or from Stones and Schirrus's in the Lungs : But the more Notable Cause is the Convulsions of the Organs of Respiration, especially the Diaphragm, occasion'd by the disorders of the lower Belle. as in Hysterick or Hypochondriac

Fig. 2. *The Practice of Physick*. Page 153. By Michael Etmuller, London, 1699.

irregular motions, enter inordinately into the fibres, as well as nerves, as moving of the organs of breathing."

In his *Practice of Physick*, published in 1685, Dr. Willis further states, "As to the other intent of curing in fits of the asthma, the organs of respiration being reclaimed from the convulsions they are fallen into, return *calmly* to their ordinary functions. We must use anticonvulsive and anodine remedies ; for medicines wont to be given in hysterick passions are also proper in convulsive asthma."

We find in *A Practice of Physick* (1699) that Michael Etmuller⁶ gives "sudden fear" as one of the causes of asthma, and he prescribes as cures, "... appeasing the spirits, strengthening the nerves" (Fig. 2).

Of even greater interest is the case history given in Sir John Floyer's⁷ *A Treatise of the Asthma*, written in 1726, in which he makes direct connection between an asthmatic attack induced by an infection and the pathologic residue now considered bacterial allergy intensified by a superimposed emotional disturbance.

"If I may give some rationale on this lady's asthma, I believe the intermitting fever laid the foundation of it; and the reliques of that by the trouble mentioned was turned into the nerves and gave her hysteric fits, and those being disturbed by the smoak of tobacco which is yet extremely offensive to her if she smell it; or else, the disposition of her father laid the foundation of an hysteric asthma which at present receives no relief by steel or hysteric medicines . . ."

This certainly foreshadows the psychosomatic point of view! Further quoting Dr. Floyer (Fig. 3):

"I will next describe the effect of passions in producing the fit . . . The passion of anger makes the spirits restless and apt to produce the fit; and the asthmatics observe in themselves great restlessness of spirits

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the day preceding the fit; Hippocrates' Aphorism advises all asthmatics to abstain from anger and shouting.

"Fear, solicitude and much study, discomforts the spirits and produces a restlessness in them which may occasion a fit.

"Study inflames the spirits and too much rarefies them; and all violent

I will next describe the Effect of *Passions* in producing the Fit. A Fatal Orthopnoea is described by *Forestus* from a Fright.

The *Passion of Anger* makes the Spirits restless, and apt to produce the Fit; and the Asthmatics observe in themselves great Restlessness of Spirits the Day preceding the Fit; *Hippocrates's Aphorism* advises all Asthmatics to abstain from Anger and Shouting.

Fear, Sollicitude, and much Study, discomposes the Spirits, and produces a Restlessness in them, which may occasion a Fit; the Asthmatics are commonly Hypochondriacal, which the frequent Fits produce, though that is supposed to depend on the other.

Sadness stops the Motion of Humours, and makes them more viscid. 'Tis observed, that all Asthmatics being angry or sad, do fall into Fits oftener than when they are cheerful.

Fig. 3. *A Treatise of the Asthma*. Page 137. By John Floyer, London, 1726.

emotions of the spirits quicken the pulse and thereby produce the asthma and ephemera.

"Sadness stops the motion of humours and makes them more vivid. 'Tis observed that all asthmatics being angry or sad, do fall into fits oftener than when they are cheerful."

That asthma might be caused by "nervous disorders" then received increased consideration by physicians. For example, in 1768, John Millar,¹² in his *Observations on the Asthma and the Hooping Cough*, writes of asthma (Fig. 4): "It is sometimes difficult to distinguish from the *globus hystericus* and other complaints comprehended under the general title of nervous disorders."

There were, nevertheless, as now, dissenting voices. In *Observations on the History and Cure of the Asthma*, published in 1793, Michael Ryan¹³ says, in defense of his theory that cold is

the main cause of asthma, "... Dr. Willis ... who made so material a change in the pathology of asthma and considered it in every respect a nervous disease, gives us notwithstanding a case of convulsive asthma that evidently arose from cold."

It is sometimes difficult to distinguish it from the globus hystericus, and other complaints, comprehended under the general title of nervous disorders; but as the treatment in both is similar, a mistake of this kind will seldom be attended with any bad consequence. To recount the minute distinctions is unnecessary, as they may be inferred from the description of the disease: it must, however, be observed, that tho' respiration is often affected by nervous complaints, yet in these, the spasms are not so violent, nor the breathing so laborious.

In fact, the violence of the symptoms during the paroxysm, and the almost total absence of them in the remission, together with their irregular succession to each other, are the principal diagnostic signs of the disease.

Fig. 4. *Observations on the Asthma and on the Hooping Cough.* Pages 26, 27. By John Millar, London, 1768.

A Practical Inquiry into Disordered Respiration, written by Robert Bree³ in 1800, confirms and expands Dr. Floyer's concepts (Fig. 5):

"The disposition which predisposes to asthma is the choleric. . . . Persons of this temperament are more subject to accumulations of blood in the pulmonary vessels and to be affected by sudden impulses of passion and emotion of the mind, which readily occasion an impetus in the circulation overpowering the contractile tone of the exhalants. . . . The passions of the mind may excite a paroxysm or strengthen the predisposition to it. . . . Love, grief, terror appear to distress the mind and relax the habit; they may not in this view so frequently excite the paroxysm as they may add to the predisposition to it."

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"Every sensation of the body raises a perception or idea of the mind which being recalled by the memory or imagination brings back the sensation combined with it: if a complex idea be recalled complicated sensations may be revived."

The *Passions* of the mind may excite a paroxysm, or strengthen the predisposition to it.

Anger throws its effects on the circulation whenever it occurs. The fluids separated from the blood, are determined to their excretories in greater haste, and in larger quantity. Hence a redundancy of saliva, and of bile, and a straits in breathing, are not uncommonly the result of an impetuous fall of anger. The Dyspeptic disposition is still more certainly encreased. *Joy* encreases the vigour of the heart and arteries, and by impelling the circulation before circumstances have allowed the contractile power of the exhalents of the lungs to be restored, their orifices may let the serum escape. *Love, Grief, Terror*, appear to distres the mind and relax the habit, they may not in this view so frequently excite the paroxysm, as they may add to the predisposition to it.

Every sensation of the body raises a perception or idea of the mind, which being recalled by the memory or imagination, brings back the sensation combined with it: if a complex idea be recalled, complicated sensations may be revived.

Thus the irritating cause of Asthma makes a sensation of the body, creating a perception or idea of the mind, which may be associated with other ideas. If any one of these be recalled by memory, others may be restored, and with some of them the corresponding sensations of the body, or irritated organ; and thus, the very emotions of mind, or the muscular contractions of the body, which such sensations had before occasioned, may return.

Fig. 5. *A Practical Inquiry Into Disordered Respiration.* Pages 174, 175. By Robert Bree, Birmingham, 1800.

The foregoing paragraph foreshadows the accepted significance of the part played by repression and conflict in enhancing the intensity of physical symptoms.

In 1860 in *Asthma: Its Pathology and Treatment*, by Henry

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Hyde Salter,⁴¹ a more modern phraseology appears: "What I shall endeavor to show is this: that asthma is essentially, and with perhaps the exception of a single class of cases, exclusively a nervous disease; that the nervous system is the seat of essential pathological condition." Dr. Salter lists the following as causes of asthma, proving, he states, that it is of nervous origin: fatigue, physical exhaustion, sudden or violent emotion, venereal excitement. He recommends antispasmodics, sedatives and direct nervous depressants as remedies to asthmatic attacks, and, as further proof of neurotic involvement cites the case of a man who was suffering from an acute attack of asthma, but was cured of it immediately when the need arose to administer to his sister who had an accident.

In 1879, recognition of nervous tension as a factor in bringing on asthmatic attacks is revealed in a case history presented by John C. Thorowgood⁴⁵ in *The Lettsomian Lectures on Bronchial Asthma*. Here he describes how an asthmatic attack was obviously brought on by anxiety and immediately cured when the anxiety was removed.

"My own observation," says Dr. Thorowgood, "has shown me that a most severe fit of bronchial asthma . . . may develop in the space of two minutes."

". . . A youth going up for examinations is breathing with comfort when the anxiety due to the non-arrival of the carriage . . . causes a speedy attack of asthma, which subsides as the carriage draws up to the door."

These early observations were soon to be, with a few exceptions, overshadowed by the adoption by medicine of the new laboratory techniques of pure science, and by the systematic explorations of Freud into the unconscious.

The reader may wonder why the influence of Freud and his explorations into the unconscious, and the way in which new laboratory techniques have influenced allergic reactions, are not also introduced at this time. It would be difficult, even in an outline, to describe the extraordinary and stimulating researches of the last five decades. References to these are given in the paper, "Psychodynamics and the Allergic Patient." Each of these topics, the rise of modern immunology and the rise of modern psychoanalytic psychology, represent historic fields of progress in medicine which at present must be studied separately and then synthesized by the clinician in theory and in practice.

SUMMARY

The early history of pollen hay fever discloses that in the 17th and 18th Centuries two distinct clinical syndromes were connect-

ed with the blooming of the rose. One of these is characterized by a profound general reaction of the patient accompanied by constitutional symptoms, like fainting, and is unconnected with allergic rhinitis as we know it today. The other is characterized by local nasal and ocular symptoms occurring at the time when the roses were in bloom. These symptoms were similar to hay fever as we know it today. Whereas, the first general type of reaction was connected with the presence of roses, the second hay fever type was not connected with the presence of roses but usually with the time of their blooming.

By the middle of the 19th Century the view that roses were of significance in the production of hay fever became less common, whereas dust, hay, smoke, chills and anxieties became more important. Although the term "rose fever" is used today, the general reactions ascribed to the rose have essentially vanished from the medical literature.

The relationship of the early symbolic significance of the rose with indecisiveness, effeminacy and ineffectuality is discussed in connection with the "rose fever" syndrome.

The early recognition that anger and hostility influences the asthmatic paroxysm goes back at least to the time of Hippocrates. This concept persisted through the Middle Ages without correlation with known physical causes. Emotional aspects were still emphasized in the 18th Century. The relationship to infection and pathologic residues was pointed out, and the notion of superimposed emotional disturbances was introduced. By the beginning of the 19th Century, the notion of repressed emotions entered into the discussion of the causation of asthma. However, these early observations were soon brought into line with the immunologic information accumulating in connection with pollen studies on hay fever. On the one hand, the rise of modern immunology, and on the other hand, the acceptance of psychoanalytic psychology, led to the more modern points of view which have developed primarily in the last one-half century. These two fields now remain to be synthesized by the clinician in theory and in therapy.

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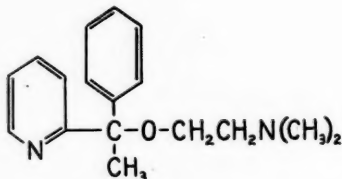
(Continued on Page 147)

THE EFFECTS OF DECAPRYN SUCCINATE, A NEW ANTIHISTAMINE
AGENT, IN SOME NATURAL AND ACQUIRED
HYPERSENSITIVITIES IN ANIMALS

2-[α -(2-Dimethylaminoethoxy)- α -Methylbenzyl]-Pyridine Succinate

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DECAPRYN Succinate is the trade name of 2-[α -(2-dimethylaminoethoxy)- α -methylbenzyl]-pyridine succinate, a new histamine antagonist. Its base has the following structure:



Results of pharmacologic studies¹ have demonstrated that this substance is a potent antihistamine agent with low toxicity. It antagonizes an average of up to 200 LD_{100s} of histamine diphosphate when injected intravenously and 143 LD_{100s} when administered orally. Doses necessary to antagonize 4 to 7 LD_{100s} of histamine are less than 0.5 mg./kg. intravenously and subcutaneously and 10 mg./kg. orally, and lethal doses by these routes are sixty-four or more times the effective doses. Decapryn Succinate effectively antagonizes the depressor response of cats and the pressor response of rabbits to histamine, and single oral doses protect rabbits against the histamine whealing response for periods of eight hours or longer. It has some antagonistic action to acetylcholine and exhibits strong local anesthetic properties of long duration when infiltrated along with epinephrine in experimental animals.

The present studies were undertaken to determine the effects of Decapryn Succinate on certain anaphylactic phenomena, because it is recognized that antihistamine activity is not necessarily a measure of activity against various types of anaphylactic and allergic reactions. These studies are of interest also because results of clinical investigations of Decapryn Succinate will permit correlation of experimental and clinical data.

PASSIVE ANAPHYLAXIS IN GUINEA PIGS

The effect of the new antihistamine on typical serum anaphylaxis was studied in guinea pigs. Twenty-six animals were passively sensitized by the intraperitoneal injection of 1.0 c.c. of antibeef serum obtained from

From the Pharmacology Department, Research Laboratories, Wm. S. Merrell Company, Cincinnati 15, Ohio

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rabbits which had received 1.0 c.c. of beef serum intravenously three times a week until the precipitin titer reached 1:20,000.

All guinea pigs were challenged forty-eight hours after sensitization with an intravenous injection of 1.0 c.c. of the beef serum antigen. Two groups of eight and nine animals were given 2 and 4 mg./kg., respectively, of Decapryn Succinate intraperitoneally twenty minutes before the challenging injection. Nine guinea pigs served as positive controls and received no Decapryn Succinate. All animals were observed for six to eight hours or until the survivors had completely recovered.

TABLE I. EFFECTS OF PRETREATMENT WITH DECAPRYN SUCCINATE INTRAPERITONEALLY ON THE RESPONSE OF PASSIVELY SENSITIZED GUINEA PIGS TO A CHALLENGING INJECTION OF BEEF SERUM

Decapryn Succinate mg./kg.	No. Animals	No. Deaths
None	9	8
2	8	0
4	9	3

Eight of nine guinea pigs (Table I) which received no Decapryn Succinate died in anaphylactic shock within five minutes after the challenging injection. Pretreatment with 2 and 4 mg./kg. of Decapryn Succinate decreased the mortality rate to an average of three in seventeen for the combined dose levels, and prolonged survival times to one hour or longer. Eight of the seventeen treated animals showed only minimal symptoms consisting of either mild dyspnea or slight body paralysis. Symptoms in the other nine animals were more severe, but they were not as severe as those in untreated animals.

HISTAMINE TOXICITY AND ACTIVE ANAPHYLAXIS IN THE MOUSE.

Mayer and Brousseau⁷ have reported experiments which they interpreted as indicating a synergism between the lethal effects of triplennamine hydrochloride and histamine diphosphate. Loew⁸ has criticized these experiments on the basis that injection volumes were excessive and may have contributed to lethal effects.

The possibility of a synergism of this type was reinvestigated employing Decapryn Succinate and histamine diphosphate. Volumes of histamine diphosphate solutions for intravenous injection ranged between 0.2 and 0.45 c.c., for 18- to 22-gram mice, and the rate of injection was 10 mg. per minute. Decapryn Succinate was injected subcutaneously fifteen minutes before the histamine in doses equivalent to approximately one-eighth and one-half of the subcutaneous LD₅₀. It was found (Table II) that the subcutaneous administration of 175 mg./kg. of Decapryn Succinate decreased the intravenous LD₅₀ of histamine diphosphate from

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1,185 to 820 mg./kg. A consideration of the standard errors in Table II indicates this difference may not be significant. A smaller dose of 50 mg./kg. of Decapryn Succinate had no effect on histamine toxicity.

TABLE II. LD₅₀ VALUES AND STANDARD ERRORS OF INTRAVENOUSLY ADMINISTERED HISTAMINE DIPHOSPHATE FOR NORMAL MICE AND FOR MICE INJECTED SUBCUTANEOUSLY WITH DECAPRYN SUCCINATE DETERMINED BY THE METHOD OF MILLER AND TAINTER (8)

Decapryn Succinate mg./kg.	Histamine Diphosphate mg./kg.
None	1185 ± 65
50	1125 ± 47
175	820 ± 38

TABLE III. EFFECTS OF PRETREATMENT WITH DECAPRYN SUCCINATE SUBCUTANEOUSLY ON THE RESPONSE OF ACTIVELY SENSITIZED MICE TO A CHALLENGING INJECTION OF BEEF SERUM

Decapryn Succinate mg./kg.	Number of Deaths Number Challenged	Mortality Per Cent
None	15/30	50
50	9/30	30
175	15/28	53.5

Mayer and Brousseau⁷ reported that while triplennamine increased histamine toxicity it had a certain protective power against mouse anaphylaxis. Decapryn Succinate was investigated to determine its effects on anaphylaxis in this species. Mice were actively sensitized by four 1.0 c.c. intraperitoneal injections of beef serum given at forty-eight-hour intervals. Twenty-one days later the mice were separated into three groups of twenty-eight to thirty each. The first group received the challenging injection only and served as the control. The second group received 50, and the third 175 mg./kg. of Decapryn Succinate subcutaneously fifteen minutes before a challenging intravenous injection of 1.0 c.c. of beef serum.

Fifty per cent of the mice which received no Decapryn Succinate died within twenty to fifty minutes after the challenging injection (Table III). Fewer deaths occurred in the group pretreated with 50 mg./kg. of Decapryn Succinate; however, the difference probably is not significant. The subcutaneous injection of 175 mg./kg. of Decapryn Succinate did not alter the mortality rate. It is apparent, therefore, that this antihistamine afforded little or no protection against anaphylaxis in the mouse under these experimental conditions.

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TABLE IV. EFFECTS OF PRETREATMENT WITH DECAPRYN SUCCINATE ORALLY ON THE RESPONSE OF RATS TO A 1.0 C.C. INTRAPERITONEAL INJECTION OF EGGWHITE

Decapryn Succinate mg./kg.	No. Rats	Responses 1½ Hours after Eggwhite	
		Marked Edema	Slight or No Edema
None	20	20	0
75	15	6	9
150	25	2	23

TABLE V. EFFECTS OF REPEATED ORAL DOSES OF 150 MG./KG. OF DECAPRYN SUCCINATE ON THE RESPONSE OF RATS TO A 1.0 C.C. INTRAPERITONEAL INJECTION OF EGGWHITE

Treatment	No. Rats	Number of Slight to Marked Reactions at Various Intervals After Eggwhite Hours			
		1½	3½	5½	12
None	10	10	9	9	8
Decapryn Succinate	10	1	2	3	0

HYPERSENSITIVITY OF THE RAT TO EGGWHITE

The white rat responds to a single parenteral injection of eggwhite with a rapidly developing edema which persists for approximately twelve hours. Léger and co-workers⁴ have recently established that this reaction is one of natural hypersensitivity and have tentatively classified it as anaphylactoid in nature. They also investigated the effects of various antihistamines on the eggwhite reaction;³ however, only about one-third of their control rats showed strongly positive reactions, and thus the antihistamines were not subjected to a severe test. It was found in this laboratory that a 100 per cent incidence of severe reactions was obtained by using larger doses of eggwhite (Tables IV and V).

In these experiments, lyophilized eggwhite, reconstituted to the original weight with water, was injected intraperitoneally in a standard dose of 1.0 c.c. An initial hyperemia developed within thirty minutes followed by marked edema of the face, feet, and ears about ninety minutes after injection. The edema began to subside four to six hours later and had completely disappeared by the next day.

A single oral dose of 150 mg./kg. of Decapryn Succinate, given forty-five minutes before the eggwhite, decreased the incidence of marked edema responses from twenty in twenty, to two in twenty-five, ninety minutes after the eggwhite injection (Table IV). Sixty per cent of the rats pretreated with a single 75 mg./kg. dose were protected for the same period. Edema developed more slowly in the two treated groups, but the degree and incidence was similar in treated and untreated animals three and one-half hours after administration of eggwhite. Twelve hours after injecting

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TABLE VI. SCORING CODE FOR SKIN REACTIONS

Value	Size, mm.	Shade	Elevation	Stage of Necrosis
1	5 to 8	almost colorless	flat	yellow-white center
2	8 to 13	faintly pink	faintly elevated	yellow center
3	over 13	pink	slightly elevated	livid center
4		red	elevated	necrotic center
5			markedly elevated	

the eggwhite the edema was still marked in eight of the ten control rats but had almost completely disappeared in both groups of treated animals.

Repeated oral administrations of 150 mg./kg. of Decapryn Succinate given forty-five minutes prior to, and two, four, and eight hours after, the eggwhite injection completely inhibited the response to eggwhite in seven of ten treated rats (Table V). Two of the three positive responses were delayed in onset. Twelve hours after the eggwhite injection all treated rats showed negative or minimal reactions, whereas eight of ten control animals still showed a marked edema.

EXPERIMENTAL SKIN SENSITIZATIONS

The effect of Decapryn Succinate on experimental contact dermatitis was studied in guinea pigs which had been sensitized either to 2,4-dinitrochlorobenzene or to p-nitrosodimethylaniline. Uniform sensitizations were obtained with these chemical antigens. The criteria of sensitization were taken to be the absence of dermal reaction to sensitizing injections and the occurrence of a strong inflammatory response upon challenging intradermally with the antigen. The degree of severity of the allergic lesions was measured according to a rigid scoring code, adapted from that of Landsteiner and Jacobs,² outlined in Table VI. A score of sixteen is theoretically possible with this code, but it was never obtained because necrosis followed erythema and edema by several days.

2, 4-Dinitrochlorobenzene, Treatment with Oral Decapryn Succinate

Sensitization was induced by the intradermal injection of 0.2 c.c. of a 0.00125 per cent solution of the compound daily for ten consecutive days. Dermal sensitivity was tested after a two-week waiting period by an intradermal injection of 0.01 mg. of the compound in a 0.1 c.c. volume. Three days later the sensitized animals received a second challenging injection. Ten untreated guinea pigs served as controls, and two groups of eight each were given 40 and 160 mg./kg., respectively, of Decapryn Succinate orally twenty minutes before the challenging injection and at eight-hour intervals for the following forty-eight hours.

Lesions in untreated guinea pigs developed rapidly and sixteen hours after the challenging injection were 1 to 2 centimeters in diameter, erythematous, and infiltrated. Yellow to livid centers appeared during the following forty-eight hours, and all lesions were necrotic by the sixth day after injection.

The effect of repeated oral administrations of Decapryn Succinate on

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TABLE VII. EFFECTS OF REPEATED ORAL DOSES OF 40 AND 160 MG./KG OF DECAPRYN SUCCINATE ON AVERAGE SCORES OF LESIONS PRODUCED BY THE INTRADERMAL INJECTION OF 0.01 MG. OF 2, 4-DINITRO-CHLOROBENZENE IN SENSITIZED GUINEA PIGS

Decapryn Succinate mg./kg.	Animals No.	Average Scores at Various Time Periods Hours				
		8	16	24	48	72
None	10	10.9	11.1	10.6	9.0	9.0
40	8	5.5	8.1	5.8	6.6	7.7
160	8	3.6	4.8	5.8	4.6	4.2

TABLE VIII. EFFECTS OF REPEATED ORAL DOSES OF 40 AND 160 MG./KG. OF DECAPRYN SUCCINATE ON THE DEVELOPMENT OF VARIOUS STAGES OF SKIN LESIONS PRODUCED BY THE INTRADERMAL INJECTION OF 0.01 MG. OF 2, 4-DINITROCHLOROBENZENE IN SENSITIZED GUINEA PIGS

Decapryn Succinate mg./kg.	Animals No.	Average Period for Development Hours	
		Erythema and Infiltration	Necrosis
None	10	11	72
40	8	20	95
160	8	28	151

the dermal response to 2,4-dinitrochlorobenzene in sensitized guinea pigs is summarized in Table VII. Lesions in guinea pigs receiving repeated doses of 160 mg./kg. of Decapryn Succinate orally were only about one-half as severe as those in the controls during all periods of development as is indicated by scores in the table. Repeated oral doses of 40 mg./kg. of Decapryn Succinate were less effective.

The dermatitis also developed more slowly in treated animals (Table VIII). Guinea pigs treated with 160 mg./kg. of Decapryn Succinate developed erythema and edema an average of seventeen hours later than did the controls, and the appearance of necrosis was delayed seven days.

p-Nitrosodimethylaniline, Treatment with Oral Decapryn Succinate

Dermal sensitization was obtained in twenty guinea pigs by applying approximately 1 gram of a 5 per cent suspension of the compound in petrolatum daily for eighteen consecutive days. Two weeks later marked hypersensitivity was demonstrated by the occurrence of a severe inflammatory reaction following an intradermal challenging injection. Three days later all sensitized guinea pigs were rechallenged with a single local application of the sensitizing ointment. Seven guinea pigs were treated with 40 mg./kg. and five with 160 mg./kg. of Decapryn Succinate orally. Eight were untreated and served as controls. The drug was given twenty-minutes prior to challenging and at eight-hour intervals for the following forty-eight hours.

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TABLE IX. EFFECTS OF REPEATED ORAL DOSES OF 40 AND 160 MG./KG. OF DECAPRYN SUCCINATE ON THE DERMAL RESPONSE TO THE TOPICAL CHALLENGE OF p-NITROSODIMETHYLANILINE IN SENSITIZED GUINEA PIGS

Decapryn Succinate mg./kg.	Animals No.	Responses 96 Hours After Challenge	
		Severe No.	Mild or Negative No.
None	8	6	2
40	7	1	6
160	5	0	5

TABLE X. EFFECTS OF ONE PER CENT DECAPRYN OINTMENTS ON AVERAGE SCORES FOR LESIONS PRODUCED BY THE INTRADERMAL INJECTION OF 0.01 MG. OF p-NITROSODIMETHYLANILINE IN SENSITIZED GUINEA PIGS

Ointment Base	Animals No.	Average Score of Group Hours					
		8	24	48	72	5	7
Controls	6	11.3	10.8	8.5	9.1	6.9	5.8
Petrolatum	7	9.1	7.4	5.8	7.5	5.1	4.3
Water soluble ointment base	7	10.7	9.8	6.1	4.1	3.4	2.8

Table IX shows that repeated oral administrations of Decapryn Succinate markedly decreased the incidence of severe lesions produced by challenging topically with p-nitrosodimethylaniline. The allergic reactions in both treated and untreated animals did not increase in intensity after ninety-six hours. At this time eleven of the twelve treated animals showed only mild erythema and slightly thickened and discolored skin, whereas six of eight untreated animals evidenced severely inflamed and excoriated lesions. The absence of excoriated lesions in treated guinea pigs probably indicates that Decapryn Succinate eliminated the burning or itching of the reacting skin.

p-Nitrosodimethylaniline, Treated with Decapryn Ointments

Two weeks after the preceding study, the twenty-sensitized guinea pigs were rechallenged with intradermal injections. Six guinea pigs received no treatment. Two test groups of seven animals each were treated with local applications of 1 per cent of Decapryn base, in petrolatum or in a water-soluble ointment base, twice daily for three days. The antihistamine treatment (Table X) did not delay the appearance of the inflammatory process, as is indicated by scores at the eight-hour period; however, the inflammation subsided earlier in treated than in untreated skin. This is shown by the trend for scores to decrease more rapidly in treated groups, especially in the group treated with the water-soluble base preparation. The increase in scores at the seventy-two-hour observation period, for con-

trol animals and those treated with Decapryn in petrolatum, is accounted for by the fact that signs of early necrosis were developing in these animals before the marked erythema and edema had subsided, thereby adding to the score as determined by this scoring system. It was observed that necrosis of lesions in treated animals appeared about four days later than in untreated animals and healed seven days earlier.

DISCUSSION

The experiments reported here demonstrate that Decapryn Succinate, an antihistamine, has considerable protective action against passive anaphylaxis in guinea pigs, hypersensitivity to intraperitoneally administered eggwhite in rats, and cutaneous reactions following skin sensitization with chemical antigens in guinea pigs.

The first of these protective actions was obtained following parenteral administration. Similar effects have been demonstrated by others for other antihistamine compounds. The protective action against eggwhite hypersensitivity and experimental contact dermatitis which followed oral administration apparently is the first demonstration of oral effectiveness of antihistamines against sensitizations in experimental animals.

The significance of the demonstration that Decapryn Succinate prevents the reaction to eggwhite in rats is not readily apparent; however, since this reaction consists of hyperemia followed by massive edema, it is probable that agents which are effective against the eggwhite reaction in rats may decrease capillary permeability and prevent peripheral vascular damage associated with such reactions clinically. Thus, the eggwhite reaction may provide a simple laboratory test procedure for the development of substances possessing a high degree of beneficial peripheral vascular action. The status of this reaction as a screening test naturally cannot be established until clinical findings are correlated with laboratory results on a number of compounds.

Mayer⁶ has already pointed out that another antihistamine, triplennamine, has considerable activity against experimental contact dermatitis. He found the effectiveness to be greater with topical than with parenteral administration, and he was surprised to observe consistently fair results with triplennamine against contact dermatitis in animals since his group had obtained almost completely negative results with triplennamine in man.

The results with Decapryn Succinate in experimental contact dermatitis clearly indicate that an important degree of effectiveness follows oral administration, and contrary to the experience of Mayer with parenteral administration and topical application, local application was less effective under conditions of the experiments reported here. It is appreciated that from many standpoints the doses employed were comparatively large; nevertheless, these results added to those of Mayer lead to the hope that some of the present antihistamines or new compounds may prove valuable in contact dermatitis.

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SUMMARY

Decapryn Succinate, 2-[α -(2-dimethylaminoethoxy)- α -methylbenzyl]-pyridine succinate, has been demonstrated to protect experimental animals against both natural and acquired hypersensitivities and anaphylaxis.

Intraperitoneally administered Decapryn Succinate protects passively sensitized guinea pigs against anaphylaxis, while subcutaneously administered Decapryn Succinate has little if any effect on either anaphylaxis or histamine toxicity in mice.

Single oral administrations prevent the edema response of rats to eggwhite for short periods, and repeated oral administrations almost completely suppress the response.

Local applications and repeated oral administrations markedly reduce the incidence of severe cutaneous reactions in sensitized guinea pigs challenged intradermally and topically with chemical antigens.

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EXPERIMENTAL STUDIES ON ACUTE DISSEMINATED ENCEPHALITIS IN THE RHESUS MONKEY

(Continued from Page 109)

consistently negative, although as much as 200 ml. of such serum has been injected into a single monkey, as have similar attempts using sera of rabbits injected with emulsions of monkey brain with adjuvants. Negative results were also obtained when cellular transfer with peritoneal exudates and suspensions of spleen and lymphoid tissue from affected monkeys was carried out.

STUDIES ON EGGWHITE SENSITIVITY IN THE RAT

Influence of the Endocrine Glands

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THE rat has been recognized as a species possessing naturally a certain degree of resistance to anaphylaxis. Arthus,³ Longcope,³⁵ Eberth⁸ and Almon and Parsons² have reported that anaphylaxis could not be elicited in this animal, while Parker and Parker,⁴² Suden,⁶² Pratt,⁴⁵ Molomut,⁴⁰ Weld and Mitchell⁶⁸ and Hochwald and Rackemann²² have presented evidence that symptoms of shock and even death could be obtained. In the course of their experiments with eggwhite, Parker and Parker⁴² reported some difficulty in interpreting the symptoms due to anaphylaxis from those due to the toxicity of this protein. These authors reported that all the rats—sensitized and unsensitized to eggwhite—reacted almost identically; the effects consisted mostly of a mild congestion of the lungs and intestines. In 1937, Selye⁵⁶ noticed also in the rat a peculiar reaction following an intraperitoneal injection of fresh eggwhite; it was characterized by an edema of the face, tongue, paws and clitoris, accompanied by hyperemia. More recently we have studied some factors influencing this reaction³² and have suggested that it be considered as a natural hypersensitiveness of the rat and classified as an anaphylactoid reaction.³³ In the present paper we wish to report further investigations, mainly the effects of endocrine factors and the fraction in eggwhite responsible for this phenomenon.

INFLUENCE OF ENDOCRINE GLANDS

Although Zondek⁷³ had suggested that in clinical allergy certain pathologic disturbances may be due to an hypersensitivity of the organism to its own hormones or the products of their metabolism, comparatively little is known regarding the influence of the endocrine glands on the course of allergic diseases. The main evidence of an hormonal influence comes from the observation that allergic manifestations may appear or disappear at the time of puberty, menopause, menstruation or pregnancy.^{11, 20} On the other hand, numerous experiments support the contention of an endocrine influence upon anaphylaxis; the role of the pituitary,⁴⁰ thyroid,²² adrenals^{15, 70} and pregnancy^{36, 46} has been investigated in the rat. Since the egg-white reaction resembles allergic phenomena more closely than does anaphylaxis, it provided us with the opportunity to evaluate experimentally the possible hormonal influence on this anaphylactoid reaction. This has been accomplished by observing the effects of the extirpation of the glands and the parenteral administration of hormones.

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TABLE I. INFLUENCE OF THE PITUITARY, THE THYROID AND THE ADRENALS ON THE EGGWHITE REACTION

Groups	No. of Animals	Treatment	Response	
			% Incidence	% Severity
I	10	80	53
II	14	Hypophysectomy	57	22
III	13	LAP* 20 mg/day	54	25
I	18	61	36
II	38	Thyroidectomy	31	14
III	24	Thyroxine 100 γ /day	Fatal shock (9); severe but non-fatal shock (9); hyperemia (6)	
I	9	66	28
II	10	Cortin** 0.6 c.c./day	80	27
III	20	Adrenalectomy	75	Fatal shock (11)

*Lyophilized anterior pituitary.

**Aqueous adrenal cortical extract containing 30 dog-units per c.c.

Pituitary Gland.—Fourteen male albino rats weighing 110 to 130 gm. were hypophysectomized through the retropharyngeal route and given a diet rich in carbohydrates. Nine days following this operative procedure, a single dose of 0.5 c.c. of fresh eggwhite was administered intraperitoneally to these animals as well as to those of a group of non-operated controls. They were examined at various intervals for symptoms of edema and possibly of shock, since Molomot⁴⁰ found an aggravation of anaphylaxis under the same conditions. In the case of edema the results are expressed in percentage of incidence and severity. The degree of severity is read on the face and paws according to an arbitrary scale of 0 to +++ and expressed as a percentage of the maximum possible. This method was used throughout all the experiments reported in this paper. Not only were no symptoms of shock observed, but the results given in Table I suggest that hypophysectomy exerts a lowering effect on the incidence as well as on the severity of the edema.

In an effort to determine whether a retardation in the absorption of eggwhite could be held responsible for the decrease in sensitivity, the same animals received a few days later an intravenous injection of 0.5 c.c. of eggwhite. No incidence of shock was observed and the results differed in no respect from the previous ones. Following these experiments, the animals were sacrificed. The completeness of hypophysectomy was ascertained by (1) a lowered growth curve, (2) the absence of pituitary fragments at the examination of the sella turcica, and (3) the atrophy of the testis and adrenals.

The influence of pituitary hormones was studied in normal rats treated with a preparation of cattle anterior-pituitary glands. Thirteen male albino rats weighing 110 to 130 gm. received a daily dose of 20 mg. of lyophilized glands (LAP). This amount was dissolved in 0.4 c.c. of a physiologic saline solution containing 10 per cent alcohol and administered in two daily injections. On the thirteenth day of treatment, these animals,

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as well as untreated controls, received an intraperitoneal injection of 0.5 c.c. of fresh eggwhite. The results expressed also in Table I show a slight decrease in the percentage of incidence and severity of edema. Since these values are of the same order as those obtained after hypophysectomy, it is doubtful whether they are significantly different from the normal values.

Thyroid Gland.—Among the endocrine glands, the thyroid has been given much attention in the study of the interrelationship between the glandular system and the phenomena of hypersensitivity. On the basis of experimental facts, we may now definitely assume that the thyroid gland has an influence upon the course of the anaphylactic reaction.^{23, 29, 30} Furthermore it has been recently claimed that certain allergic conditions such as urticaria, hay fever and angioneurotic edema are associated with hypothyroidism, while asthma is more frequently associated with hyperthyroidism.¹⁰

Male albino rats were divided into three groups. Animals of Group I were kept as controls; those of Group II were thyroidectomized and those of Group III were treated with thyroxin. Thyroxin in the form of sodium thyroxinate was injected daily in a dose of 100 γ contained in 0.1 c.c. of water. On the thirteenth day after the surgical intervention, or the beginning of treatment, the experimental and the control animals received an intraperitoneal injection of 0.15 c.c. of eggwhite. The results are summarized in Table I. In the thyroidectomized animals there was an obvious decrease in the incidence and severity of the edema. There was furthermore a delay in its appearance: the edema reached its maximum approximately four hours after the injection as compared to two hours in the controls. In the group treated with thyroxin, the symptoms were strikingly different. Within a few minutes most of the animals presented a shock-like condition which caused death in 37 per cent. This shock was characterized by the following symptoms: decrease in spontaneous motility, dyspnea, weakness, cyanosis, coma and finally death. Postmortem examination did not reveal anything other than a hyperemia and edema mostly localized to the small intestine; the Peyer's patches contrasted with the rest of the organ. Although 25 per cent of the animals did not show any symptoms of shock, hyperemia of the face, paws and ears was observed. No edema was present. Such a dramatic modification of benign reaction resembling angioneurotic edema was unexpected, especially in view of the fact that a dose of only 0.15 c.c. of eggwhite was sufficient to elicit this course of events.

Adrenal Glands.—Since these glands are associated with general resistance of the organism, adrenal deficiency is accompanied by an increased susceptibility to any damaging agent. Selye⁵⁶ has already shown that injection of eggwhite to adrenalectomized rats caused a very marked edema

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TABLE II. INFLUENCE OF SEX HORMONES ON THE EGGWHITE REACTION

Groups	No. of Animals	Treatment	Response	
			% Incidence	% Severity
I	10	71	40
II	29	Ovariectomy	72	48
III	20	Ovariectomy		
IV	6	Estradiol 0.5 mg./day	30	11
		Ovariectomy		
V	10	Progesterone	66	33
		5. mg./day		
VI	9	Castration	90	41
VII	8	Castration	88	42
		Testosterone		
		2 mg./day	50	18

and cyanosis. Although nine out of twelve animals died within forty-eight hours, it is difficult to evaluate accurately the effects of the operation on the response to eggwhite since no control group of untreated adrenalectomized rats was mentioned.

Male rats were adrenalectomized and injected for five days with a maintenance dose of adrenal cortical extract*. Treatment was then discontinued in order to elicit a simultaneous and equal degree of insufficiency in all the animals. Twenty-four hours later they received an intraperitoneal injection of 0.5 c.c. of eggwhite. Most of the animals developed a severe subcutaneous edema of the face and paws, followed by symptoms of shock; eleven animals out of twenty died within eight hours, while all the adrenalectomized controls survived during the same period of time.

Experimental hypercorticalism was achieved by injecting intact animals with three doses of 1 c.c. each of cortin* equally spaced during a period of five hours. Following the administration of eggwhite, we did not observe any protective effect. Similar results were observed in rats pretreated with adrenal cortical extract, 0.2 c.c. administered three times a day for ten days.

The results of these experiments may indicate that the adrenal cortex does not play any specific role in the anaphylactoid reaction, since the only evidence is a decrease of resistance following adrenalectomy. With overdosage, we did not observe any increase in the resistance of the animals to the noxious effects of eggwhite.

Sex Glands.—In a previous paper³² we reported that female rats seemed less sensitive to eggwhite than males. Furthermore, allergic phenomena are in some cases definitely influenced by the normal or pathologic activity of the sex glands.¹¹

Albino rats weighing 110 to 130 gm. were divided into seven groups: two control groups and five experimental groups. Details concerning the operative procedures and the treatment as well as the number of animals are indicated in Table II. Estradiol, progesterone and testosterone in oil

*Cortin from the Connaught Laboratories (Toronto) containing 30 dog-units per c.c.

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TABLE III. INFLUENCE OF THYMECTOMY, PARATHYROID HORMONE AND PREGNANCY ON THE EGGWHITE REACTION

Groups	No. of Animals	Treatment	Response	
			% Incidence	% Severity
I	9	64	37
II	9	Thymectomy	55	24
I	8	63	39
II	11	Parathyroid hormone 0.3 c.c./day*	72	43
I	9	66	46
II**	8	75	31

*Parathormone (Eli Lilly) containing not less than 100 U.S.P. Parathyroid units.

**Pregnant animals.

were given daily in doses of 0.5, 5.0 and 2.0 mg. respectively, administered in two subcutaneous injections. After a period of twelve days, all the animals received 0.5 c.c. of eggwhite. From the results expressed in Table II, it appears that ovariectomy or castration has no effect. Estradiol decreases the sensitivity of the animals, and testosterone is also effective to a certain degree. Progesterone has no effect. Although the differences between the values in Groups I and V, II and VI, and III and VII are not statistically different, it is interesting to note that in all cases the incidence of edema is less marked in the female groups than in the corresponding male groups. This would tend to confirm the previous observation that females are more resistant than males. It should be also mentioned that at autopsy the adrenals of the estradiol treated rats were markedly enlarged and brown, suggesting an increased activity of these organs.

INFLUENCE OF OTHER ENDOCRINE ORGANS OR CONDITIONS

Experiments were performed on thymectomized rats, on rats treated with parathyroid hormone and on pregnant rats.

Rats were thymectomized and kept without treatment during a period of six days when recovery was complete. Another group received a daily dose of 0.3 c.c. of parathyroid hormone (ca. 33 U.S.P. parathyroid units) divided in two subcutaneous injections, for a period of twelve days; this amount was sufficient to cause hyperparathyroidism since calcium deposits were found in organs at autopsy. Then all the animals, as well as controls of the same body weight, received 0.5 c.c. of eggwhite. The results contained in Table III indicate no significant influence of the thymus and the parathyroids. Experiments on pregnant rats during the second half of pregnancy, when the hormonal secretions are at their maximum did not show any difference from controls of the same body weight.

INFLUENCE OF DAMAGING AGENTS

Selye⁵⁶ reported that during the alarm reaction produced by formalin, animals are more resistant to eggwhite. We decided to extend these

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TABLE IV. INFLUENCE OF ALARMING AGENTS ON THE REACTION TO EGGWHITE

Groups	No. of Animals	Treatment	Response	
			% Incidence	% Severity
I	10		70	35
II	16	Formalin	31	7
III	12	Exercise	33	6
IV	9	Cold	55	22
V	6	India ink	16	6

studies by the following experiment: five groups of rats were treated as follows: Group I, untreated controls; Group II, formalin; Group III, exercise; Group IV, cold, and Group V, india ink. Formalin in a 10 per cent solution was administered subcutaneously in a daily dose of 0.8 c.c. divided into four injections. Animals of Group III were forced to run during one hour in a treadmill four times a day; animals of Group IV were kept continuously in a cold room where the temperature was maintained around 3° C; and those of Group V received one intravenous injection of 0.5 c.c. of a 25 per cent solution of Higgins india ink. After twenty-four hours of treatment all the animals were injected with 0.5 c.c. of eggwhite. The results are summarized in Table IV. They indicate a definite protective effect of alarming agents on the anaphylactoid reaction, principally with formalin, exercise and india ink.

FACTORS IN EGGWHITE RESPONSIBLE FOR THE REACTION

In a previous paper³² we have shown that lyophilized eggwhite powder possessed the same properties as the fresh material. The problem was therefore to try to isolate the active principle(s) from the various components, particularly from the proteins. We tested the five distinct antigens contained in eggwhite, mainly ovalbumin, ovoglobulin, ovomucin, ovomucoid and conalbumin. The ovalbumin used, kindly supplied by Dr. A. G. Cole, was in the form of crystals. A fraction containing ovoglobulin and ovomucin was prepared according to the method of Hektoen and Cole,²¹ and ovomucoid was prepared by the method of Morner modified by Hektoen and Cole.²¹ Conalbumin was replaced by chicken's blood serum, since the last two authors showed that the two substances are immunologically and probably chemically identical. All these substances except blood serum were in a dry form; they were dissolved in a slightly alkaline sodium chloride solution.

Groups of ten male rats were injected intraperitoneally with one of these substances in the doses indicated in Table V. It should be pointed out that the doses administered were much larger than the amount normally contained in 0.5 c.c. of eggwhite. As can be seen from Table V only rats injected with ovomucoid or eggwhite presented the typical symptoms of edema. In a second experiment, animals previously sensitized with thyroxin (100 Y for twelve days) received the same substances intra-

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TABLE V. EFFECTS OF THE VARIOUS COMPONENTS OF EGGWHITE

Groups	No. of Animals	Treatment	Response	
			% Incidence	% Severity
I	10	Fresh egg-white 0.5/c.c.	70	26
II	10	Ovomucoid 15 mg.	60	30
III	8	Thyroxine 100 γ /day then ovomucoid 15 mg.	Fatal shock (6); severe but nonfatal shock (2)	
IV	10	Ovomucin-ovoglobulin fraction 10 mg.	0	..
V	10	Conalbumin (chicken's blood serum) 2 c.c.	0	..

peritoneally at the same dose level. Again only the group receiving ovomucoid reacted; of these animals all were in shock and six out of eight died.

Since ovomucoid belongs to the group of the glucoproteins, further experiments were undertaken in order to see whether the activity was due to the carbohydrate residue. Ovomucoid was treated with barium hydroxyde according to the method of Stacey and Woolley,⁶¹ and two fractions were isolated; a protein fraction and a carbohydrate fraction. These were tested as outlined previously, but did not reveal any activity. Two possibilities therefore remain: either the activity of ovomucoid is related to the whole molecule of this substance or is due to the protein residue which was to a certain degree denaturated during the chemical process. One point however seems clear, and that is the inactivity of the carbohydrate residue.

In 1907, Vaughan and Wheeler⁶⁴ reported the extraction of poisonous substances from the proteins contained in eggwhite. By injecting the guinea pigs, they produce symptoms of shock followed by the death of the animals. In view of these results, we thought that the same substance could be held responsible for the edema in the rat, the difference in the symptoms being due to the animal species. We therefore treated eggwhite according to the method used by these authors. This involved precipitation of the proteins with alcohol and extraction with absolute alcohol containing 2 per cent sodium hydroxide. Two fractions were obtained: a "poisonous" fraction soluble in alcohol and an insoluble "nonpoisonous" fraction which contains the carbohydrate residue of the protein molecule. Tested in the rat according to our method, no edema or symptoms of shock were obtained with either of the two fractions.

DISCUSSION

Inhibition of the eggwhite reaction with antihistaminic substances³¹ constitutes indirect evidence that histamine or H-substance is responsible for the edema. Since symptoms of anaphylaxis are probably due to histamine liberation and since a certain parallelism exists between the anaphylactic response of a species and its sensitivity to histamine, it would

be of interest to compare the influence of the endocrine glands on the eggwhite reaction, anaphylaxis and histamine poisoning.

Thyroidectomy causes a marked inhibition of the severity of the anaphylactic and histaminic reactions,^{9, 16, 23, 24, 29, 44, 60} while administration of a thyroid preparation or thyroxin produces an opposite effect.^{4, 22, 28, 61} Similarly, experimental hyperthyroidism increases markedly the sensitivity to the noxious effects of eggwhite. It has been suggested that the effects of thyroid overdosage could be due either to an increased release of toxic substances ("H-substance") or to an increased sensitivity of the animals.²² The first hypothesis is supported by the observation of an increased content of histamine in the tissues occurring after thyroid administration,¹⁸ and the latter is based on the fact that experimental hyperthyroidism is associated with a decreased resistance to histamine.¹⁴

Many observations suggest that the adrenals play also an important role. The experiments carried out on rats are the most convincing since shock is rarely fatal in normal animals. Adrenalectomy diminishes markedly the resistance to anaphylaxis,^{15, 27, 70} to histamine³⁷ and to eggwhite. According to Wyman,⁷⁰ this increased susceptibility would be related to a lack of medullary secretions. On the other hand, the evidence presented by Perla and Sandberg⁴³ suggests more probably that cortical insufficiency is the responsible factor. It has been also demonstrated that following adrenalectomy there is an increase in the histamine content of the tissues of the rat⁵⁰ accompanied by a decrease in the histaminase content of the lung.²⁵ The effects of adrenocortical extracts have not been thoroughly studied in the rat. The only experiments reported concerned the ability of these extracts to restore a normal response to histamine in adrenalectomized animals.^{38, 49} It has been claimed however that in the guinea-pig and the dog cortin diminishes the severity of anaphylactic shock,^{7, 69} while desoxycorticosterone is ineffective against histaminic or anaphylactic symptoms.^{19, 41} A possible explanation for the nonprotective effect of such extracts against eggwhite edema could be that the doses used were inadequate. It is known that the requirements of the rat are larger than in any other species; the maintenance dose is approximately ten to fifteen times higher in the adrenalectomized rat than in the dog.⁵⁷ Some observations suggest, however, that hyperactivity of the adrenals may be associated with an increased resistance to eggwhite edema. Rats treated with estrogens or damaging agents were more resistant to eggwhite and presented at autopsy large brown adrenals. These morphologic changes which are characteristic of the "alarm reaction"⁵⁸ constitute a sign of stimulation as demonstrated by histologic or metabolic studies.^{5, 6, 39, 65, 66, 67} It should be mentioned furthermore that Karady et al²⁶ and Gottschall et al¹⁷ have reported that anaphylaxis is inhibited by previous treatment with alarming agents. Farmer and Fribourg¹⁴ suggested that enhanced anaphylactic and histaminic responses following treatment with thyroid preparations or thyroxin are due to adrenal deficiency. They based their contention on

the observation that this treatment leads to (1) a diminution of the ascorbic acid and cholesterol content of the adrenals, (2) a hypertrophy of the adrenal cortex, and (3) a decrease or depletion of the cortin content of the cortex.¹³ The importance attached by Farmer¹³ to the determination of the cortin content of the adrenals seems exaggerated in view of the fact that the specificity of the method used has been the object of many criticisms.^{48,59} Furthermore, according to many investigators,^{34, 52, 53, 54} the diminution of the ascorbic acid and cholesterol content as well as the hypertrophy of the adrenals is not related to a deficiency but to an overactivity of these glands.

Conflicting reports have been made concerning the effects of sex glands on anaphylaxis. According to Yun,⁷¹ testis extirpation diminishes the severity of anaphylaxis while injection of a testicular suspension restores the normal sensitivity to allergens. The claim made by Schafer⁵⁵ that estradiol increases the susceptibility to anaphylaxis could not be confirmed by Farmer¹² and Vallery-Radot et al.⁶³ Similarly, pregnancy has no definite influence on anaphylaxis.¹¹ Our experiments show a definite influence of estradiol and testosterone while removal of the testis or the ovaries did not interfere with the normal reaction to eggwhite. Progesterone or pregnancy was without effect.

The fact that thymectomy⁷¹ and parathyroidectomy²⁰ diminishes the severity of anaphylactic symptoms could not be observed in eggwhite treated rats.

Molomut⁴⁰ has reported that hypophysectomized rats were highly susceptible to anaphylaxis. He attributed this influence to an altered reactivity of the operated animals, since the antibody formation was the same in the experimental and in the control groups. The finding of the present authors that hypophysectomy has no effect upon the sensitivity to eggwhite, while it increases anaphylactic symptoms, constitutes the only important difference in the influence of endocrine glands upon these two reactions. It must be remembered that the extirpation of an important organ like the pituitary is followed by many morphologic and physiologic changes in other endocrine glands which themselves have an inhibiting or accelerating influence. The effect of hypophysectomy is therefore the resultant of these antagonistic influences (e.g. thyroidectomy versus adrenalectomy) so that it is difficult to attribute any specific role to this gland.

In summary, the influence of the endocrine glands on the eggwhite reaction is, with the exception of the pituitary, quite similar to what has been found in anaphylaxis or histamine intoxication. The reaction is enhanced following thyroxin treatment or adrenalectomy, and inhibited following thyroidectomy or treatment with estrogens, testosterone and damaging agents. The influence of the adrenocortical hormones is not yet supported by sufficient evidence to permit definite conclusions.

It is significant that the active fraction of eggwhite responsible for the

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reaction contains a carbohydrate residue. Heidelberger and collaborators⁷² have called attention to the great importance of polysaccharides in the specificity of bacterial antigens. More recently Rhoden and Sutherland⁴⁷ reported that patients allergic to raw eggwhite reacted strongly to a "deproteinized product" from eggwhite constituted mainly by ovomucoid. They prepared also an active fraction from linseed and castor bean which gives a positive Molish test but a negative biuret test. By means of electrophoresis and ultracentrifugation, Abramson¹ found that the active part of various pollens responsible for hay fever were comparatively small molecules having properties similar to but not characteristic of proteins. There are indications that they are polypeptides coupled with other molecules more or less formed like carbohydrate molecules. The similarity which exists between the chemical nature of the fraction of eggwhite responsible for edema in the rat and the chemical nature of substances responsible for allergy need therefore to be emphasized.

According to Zinsser et al⁷² all forms of hypersensitiveness can be divided into two main classes: (1) hypersensitiveness in which an antibody mechanism is involved, and (2) hypersensitiveness in which no antibody mechanism has yet been demonstrated. We first explored the possibility of an antigen-antibody mechanism. All attempts to detect antibodies in the blood of normal rats by a precipitin test were unsuccessful. It must be remembered however that even in anaphylaxis, symptoms of shock may be obtained without demonstrable antibodies.⁷² Another possibility was the existence of an acute biotin deficiency. It is known that long treatment with eggwhite causes the formation of skin lesions constituting what is called "eggwhite injury."² Eggwhite injected intraperitoneally could possibly elicit an acute biotin deficiency because of its rapid absorption. Biotin was injected into rats at the dose of 1500 rat-units shortly before eggwhite administration. The incidence and the severity of the edema was in no way different from those observed in normal controls.

It is felt that all the data reported in this paper support the contention that the eggwhite reaction is a phenomenon of hypersensitiveness. Because of its similarity to certain human allergies, it could serve as a useful experimental method to approach certain problems on allergy.

SUMMARY

The influence of the endocrine glands upon the anaphylactoid reaction as elicited in the albino rats by eggwhite was studied.

The reaction was enhanced by the administration of thyroxine and by adrenalectomy.

Symptoms of shock, fatal in a certain percentage of cases were observed instead of the edema which is normally elicited.

On the other hand, the reaction was decreased after thyroidectomy, and after treatment with estrogens, testosterone or damaging agents.

Hypophysectomy, gonadectomy, thymectomy and pregnancy, adminis-

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tration of anterior pituitary preparation, of cortin, progesterone and parathyroid hormone did not have any significant influence upon the reaction.

Among the five protein fractions contained in eggwhite, only ovomucoid elicited the same symptoms as were produced by fresh eggwhite.

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RAGWEED REAGINS IN NASAL SECRETION. Max Samter and Elmer L. Becker, University of Illinois College of Medicine, Chicago, Ill. *Proc. Soc. Exper. Biol. & Med.*, 65:140-41, 1947.

The Seitz filtrate of nasal secretion of seven out of ten ragweed-sensitive patients contained reagents to ragweed which were demonstrated by passive transfer. Nasal secretion from normal persons and patients sensitive to inhalants other than ragweed gave negative results. The study was carried out within two months after the end of the ragweed season. (Author's abstract.)

VULVO-VAGINAL PRURITUS ASSOCIATED WITH HAY FEVER

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ON August 24, 1939, a five-year-old girl (Case 1) was brought to us complaining of severe coryza, conjunctivitis, and intense itching in the region of the mucocutaneous junction of the vulva and vagina, present for two weeks. The previous year she had had similar symptoms from early August until mid-October. The condition appeared to be a typical severe hay fever of the fall type, accompanied by intense itching of the vulva, occurring in two successive ragweed seasons, with freedom of all symptoms during the remainder of the year. Skin tests by the scratch method gave a marked reaction to ragweed pollen but none to the other routine allergens. She was treated co-seasonally during 1939 with frequent small doses of ragweed extract and with palliative drugs, and the symptoms gradually subsided, disappearing earlier than they had the previous season. No more pollen therapy was given after 1939, and during the subsequent ragweed seasons she had considerable coryza and conjunctivitis but no accompanying vulvitis after the age of seven.

Itching in the vagina and anus is often encountered as a part of constitutional reactions to injections of allergens. However, this symptom as a part of hay fever seemed unique and stimulated further investigation.

Although many clinicians have probably observed the occurrence of vulvar irritation as an integral part of respiratory pollinosis, little has been published concerning this syndrome. Vaughan² states: "Genito-urinary Diseases. . . . These are infrequent. They include . . . vulvar irritation and balanitis which may be due to the action of absorbed allergen or allergen locally applied as a medication or contraceptive." Feinberg³ mentions that "In three or four patients the vaginitis and vaginal itching occurred during the hay fever season in ragweed-sensitive patients."

By October, 1946, we had observed a total of eight such cases, and the pertinent data appears in Table I. In each case the history of vulvar itching was voluntarily given as a major complaint. Subsequently, 100 adult female patients who were being treated for ragweed hay fever with or without asthma were questioned but no instance of seasonal vulvar itching was discovered.

A résumé of Cases 2 to 8 follows.

CASE REPORTS

Case 2.—M. L., aged five, was seen in November, 1945, complaining of hay fever and intense vulvar itching throughout August and September of 1944 and 1945. She was relieved in air conditioned buildings, only to have a recurrence of symptoms in unfiltered air. Positive skin reactions (puncture method) were obtained with dandelion and ragweed pollen. Following perennial treatment with ragweed pollen

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TABLE I. SEASONAL VULVO-VAGINAL PRURITIS ASSOCIATED WITH RAGWEED HAY FEVER

Case	Age	Age of Onset of Vulvitis	Severity of				Hay Fever Improved After Treatment	Vulvar Pruritis Improved After Treatment	Remarks
			Rhinitis	Asthma	Conjunctivitis	Vulvar Pruritis			
1. J.L.	5	4	++	None	++++	++++	Co-seasonal treatment 1939 only		No treatment since 1939. Vulvo-vaginitis disappeared at age 7 but seasonal hay-fever continued.
2. M.L.	5	4	++	None	++++	++++			100%
3. P.K.	4	2½	++	++	+++	++++	80%	80%	Symptoms cleared in Connecticut and recurred on return to Ohio in September, 1945.
4. B.G.	6	5	+++	None	++++	+++	80%	100%	See case history.
5. S.K.	7	5½	+++	None	+++	++++	80%	100%	Vulvo-vaginitis occurred outside hay fever season after Sulfa therapy.
6 B.S.R.	4½	2½	+++	None	+++	+++	See remarks	See remarks	No pollen therapy. Moved to Arizona, August, 1946, and symptoms disappeared immediately.
7. S.Y.	11	8	++++	++	++++	++++	60%	60%	Mild perennial rhinitis and asthma.
8. M.S.	7	3	++++	None	++++	+	75%	100%	Vaginal pruritis occurred as immediate reaction to some injections of ragweed pollen.

extract, she had neither hay fever nor vulvar itching in August and September, 1946, although she stayed in Columbus during the entire season.

Case 3.—P. K., aged four, was seen in September, 1945, complaining of hay fever, asthma, and vulvar itching. Conjunctivitis and vulvar pruritus were the most harassing symptoms. She had a history of "summer colds" and vulvar itching in 1943; hay fever, asthma and vulvar itching in June and in August and September, 1944; and similar symptoms in June and August, 1945, which disappeared within three days following her arrival in Connecticut on August 20, 1945. Vulvar itching was always coincident with hay fever, especially with the conjunctivitis, and of proportionate severity. Positive skin tests (puncture method) were obtained to house dust and to the pollens of grass, ragweed, and dandelion. Following perennial treatment of these three pollen extracts, she suffered only mild hay fever and vulvar itching in early September, 1946.

Case 4.—B. G., aged six, was seen on September 11, 1944, complaining of severe hay fever, especially conjunctivitis, and severe vulvar itching, with a history of similar symptoms during September, 1943. Positive skin reactions were obtained by puncture method to ragweed, marsh elder, and pigweed pollens. Although specific pollen therapy was not given, the symptoms subsided after two weeks, and she remained well until August 20, 1945, when identical symptoms recurred. In spite of co-seasonal pollen injections, coryza and vulvitis persisted for four weeks. During 1946, pre-seasonal ragweed injections were given, resulting in complete prevention of vulvitis and only mild hay fever. On September 3 she went to Texas and had no hay fever on arrival.

Case 5.—S. K., aged seven, had a history of frequent "colds" and "bronchitis" since age five; vulvar itching at age five and one-half following "sulfa" treatment for a "bowel infection;" severe hay fever and vulvar pruritus in August and September,

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1944, and a "cold" and vulvar itching for ten days in June, 1945. Hay fever and vulvar itching, beginning August 21, 1945, were present when she was first seen by us on September 9, 1945. The skin reacted (puncture method) to the pollen of box elder, dandelion, grass, and ragweed. Perennial treatment with grass and ragweed in 1946 was followed by a symptom-free grass season. Only slight hay fever without vulvitis occurred in early September.

Case 6.—B. S. R., aged four and one-half, was seen on August 26, 1946. She had hay fever each August and September, beginning at age two and one-half (1944), and a slight perennial rhinitis. In April, 1946, she had severe hay fever whenever she played with dandelion blossoms. On August 18, 1946, severe hay fever began. Her mother stated that she had vulvar itching and dermatitis of the buttocks only when she had hay fever and in proportionate severity. A skin test was made with ragweed only, resulting in a strongly positive reaction. The family moved to Tuscon, Arizona, in mid-September, 1946, and all the symptoms immediately disappeared.

Case 7.—S. Y., aged eleven, was seen in May, 1946, with a history of severe hay fever which had occurred annually from early August until frost since age eight. She had severe vulvar itching with the hay fever but at no other time. Perennial rhinitis was a minor complaint and was not accompanied by vulvitis. Positive puncture tests were obtained with cat dander and ragweed pollen. There was mild hay fever and vulvitis during September, 1946, in spite of preseasonal ragweed injections.

Case 8.—M. S., aged seven, was seen on August 24, 1945, with a history of severe hay fever annually from August 15 to September 15 since the age of three. She had mild vaginal itching during the hay fever season only, and its severity varied with the severity of the conjunctivitis. Her skin reacted positively to ragweed pollen only. Co-seasonal treatment with ragweed, started August 24, 1945, was followed by complete disappearance of vulvitis, except on two occasions when it occurred as an immediate response to a pollen injection and continued for twenty-four hours, while the hay fever was only partially relieved. Preseasonal treatment in 1946 was followed by complete freedom from vulvitis and moderate relief of hay fever.

It is the clinical impression that these cases are relatively rare, yet when the data in Table I are given consideration, it will be seen that all our cases occurred in girls under twelve years of age, and when we limit our perspective to this age group, it is obvious that seasonal vulvar itching is quite common. Also of significance is the age of onset, which was under five in seven of twenty-four hay fever cases (about 30 per cent) and between five and ten years of age in only one of fifty-five cases. It is evident, therefore, that in most instances the difficulty will begin in girls between two and five years of age, and that the condition will probably not be encountered beyond adolescence.

Although there were no visible skin changes except those as a result of scratching, the most intense itching seemed to be in the region of the mucocutaneous junction between the vulva and vagina. Itching occurred only during the ragweed pollinating season, except in the patient in Case 3 in whom there were symptoms also during the grass pollinating season, in Case 5 following the administration of a "sulfa drug" and in Case 6 "after playing with dandelion blossoms." Response to specific treatment,

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filtered air, or change of climate was proportional to the improvement of the hay fever. One might hypothecate that occasional cases of pruritus ani might occur on the same basis, but we have encountered no such complaint during the hay fever season, although it does occur as a part of constitutional reactions to the injection of pollen extract.

No instance of pruritus of the urinary meatus in small boys, as a part of seasonal hay fever, has been observed. However, in three of fifty-two boys under five years of age, urinary frequency during the day and nocturnal enuresis were noted as occurring at the peak of the ragweed hay fever season.

SUMMARY

Eight cases of intense vulvo-vaginal pruritus, occurring in girls between the age of two and twelve as a major symptom of ragweed pollinosis, are presented. Vulvar itching responded as readily as hay fever to specific "immunization" against, or avoidance of, the offending pollen. Preseasonal pollen therapy prevents vulvar itching in most cases. Similar symptoms were not encountered in adolescent or adult females.

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TEMPORAL ARTERITIS

Case Report

MICHAEL ZELLER, M.D., F.A.C.A.
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THE syndrome of temporal arteritis was first described by Horton, Magath, and Brown⁵ in 1932. Dantes,² in a review of thirty-six cases reported to date, including one of his own, states that only twenty-seven are unquestionable instances of temporal arteritis. In attempts to classify the condition, the alleged absence of eosinophil cells in the cellular infiltrate has been mentioned as one of the factors differentiating it from periarteritis nodosa. However, Bowers,¹ in a case report, described the presence of an appreciable number of eosinophil cells in the cellular infiltrate, and Kilbourne and Wolff⁶ mention eosinophil cells as a prominent feature of the sections in their case.

The purpose of this communication is to record the third case with eosinophil cells and report the prompt recovery which followed resection of a segment of each temporal artery performed after large doses of antibiotics had failed to effect improvement.*

REPORT OF CASE

S.H., a white man, sixty-two years of age, an accountant, was admitted to the Ravenswood Hospital on September 22, 1946, with the complaints of generalized aches and pains, sore throat, headache, and difficulty in swallowing. The illness began suddenly September 1, 1946, with pains in the legs, followed a day or two later by sore throat and headache, which persisted until admission to the hospital. The patient worked for four or five days after the onset, but at the end of that time became completely disabled by the generalized "grippe-like" aches and pains. For several days after the onset, swelling of both jaws and the soft tissues of the right eye was noted, but this soon disappeared. The patient stated that he had no chill, gastrointestinal symptoms, cough, chest pain, or eye symptoms at any time. Since the onset, there had been a daily elevation of the temperature to from 99° to 100° F. accompanied by progressive weakness and malaise.

The past history included a prostatectomy seven years earlier and moderate dyspnea on exertion for the previous three months. Otherwise the patient had always been well.

On admission to the hospital, he appeared slightly cyanotic with a grayish pallor, weak, and somewhat confused mentally. He had obviously been ill for some time. Temperature was 100° F., pulse 88, and respiration 26. The temporal arteries on both sides were dilated, tortuous, pulsating, and clearly visible from the temporo-mandibular articulation upward for a distance of 8 cm. The parietal branches of the temporals were not involved. In the skin immediately adjoining the temporal arteries there were several areas of erythema from .5 to 1 cm. in length. The findings over both occipital arteries were similar.

The tonsillar areas, which the patient described as being sore, were not red or swollen, but pressure upon them produced pain. Pain in the jaw articulations of both sides and in the throat was produced by swallowing. The patient was un-

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*The author is indebted to Dr. Arthur V. Bergquist for permission to publish this case, and to Dr. Josiah J. Moore for the pathologic report.

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able to use his dental plates because of pain, although the gums were not swollen, red, or abnormal in any way. Retinal examination revealed considerable arteriosclerosis. The heart was slightly enlarged to the left, and the electrocardiogram indicated myocardial damage. The blood pressure was 130/90. Examination of

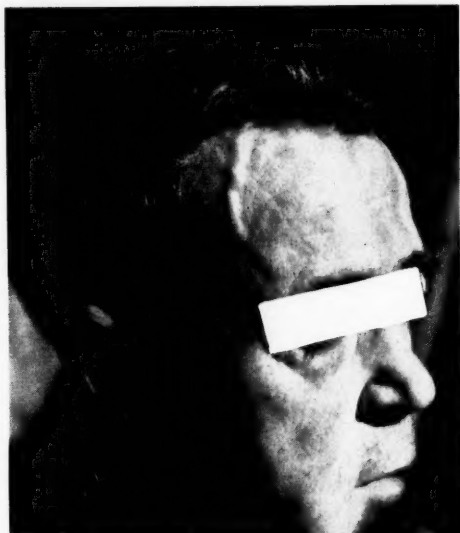


Fig. 1. Patient S. H. Distended tortuous artery prior to resection.

the lungs and abdomen was essentially negative. The deep reflexes were somewhat brisk. Palpation of the femoral, radial, carotid, and dorsalis pedis arteries revealed no pain, tenderness, or tortuosity.

On admission, the red cell count was 4,580,000 and the white cell count 24,200. The hemoglobin was 13.5 gm. The differential white cell count showed 86 mature cells, 3 immature cells, 6 lymphocytes, 3 monocytes and transitional cells, and 2 eosinophil cells. The nonprotein nitrogen was 25 mg./100 c.c. The blood Wassermann reaction was negative. The sedimentation rate was 100 mm. in 60 minutes. Blood cultures remained negative. The urine had a specific gravity of 1.022. It showed a faint trace of albumin, but was free from sugar.

On x-ray examination for study of the soft tissues of the temporal region, no evidence of calcified vessels was found. X-ray examination of both legs for soft-tissue study showed moderate calcification of the blood vessels but no tortuosity. Chest roentgenograms disclosed a calcified plaque on the arch of the aorta and marked tortuosity of the arch compatible with that of an aortitis associated with hypertension. The inner portion of the apex of the right lung showed a dense homogeneous shadow which was believed to be due to an enlarged innominate artery.

As sulfathiazole, in doses as large as 90 gr. administered daily for fourteen days prior to the patient's admission to the hospital, had failed to influence the clinical condition, penicillin in 100,000-unit doses was given intramuscularly every three hours for five days after his admission. This, too, failing to effect improvement, partial excision of the artery, which had been followed by relief in the

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cases reported by Bowers¹ and Horton and Magath,⁴ was decided upon, and on September 28 Dr. Arthur V. Bergquist removed a 2 cm. segment of each temporal artery. The pathologic report of Dr. Josiah J. Moore, the pathologist, was as follows:

"Section of the right temporal artery reveals a marked narrowing of the lumen. The intima is thickened. Some of the cells are vacuolated, and there is a diffuse infiltration of neutrophil, eosinophil, and round cells. Similar cells infiltrate the muscularis and are very dense in the adventitia. There is marked vacuolation of the muscle cells. Numerous giant cells are present in the media. The adventitia is greatly thickened, and in it are found some small nodules with necrotic centers, around which are many epithelial cells with an outer circle of round cells. The left artery shows a similar reaction. The process is therefore a diffuse arteritis."

Cultures of the ground-up excised portions of the arteries were made both aerobically and anaerobically in blood agar, brain infusion agar, and brain infusion broth, with no growth after ten days.

The excision was followed by general improvement, evidenced by increased appetite, a gain in weight and strength, and a striking gain in mental acuity with elimination of mental confusion. By October 1, the patient was ambulant and free from fever except for an occasional elevation of the temperature to 99° F. at 4 p.m. However, on October 30, the sedimentation rate was 114 mm. per hour, and repeated x-ray examination of the chest revealed continued prominence and widening of what appeared to be the innominate artery. Widening of the innominate artery, shown by the x-ray in this condition, has been reported by Dick and Freeman.³

SUMMARY

A third case of temporal arteritis with eosinophil cells, in which the diagnosis was proved by clinical and histologic examination, is presented. The failure of sulfathiazole and penicillin therapy to influence the clinical condition led to resection of a segment of the temporal arteries. The operation was followed by prompt improvement and recovery. The eosinophilic infiltration suggests that temporal arteritis may be due to an allergic mechanism or may be, after all, an atypical form of periarteritis nodosa.

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CONVULSIONS FOLLOWING EPINEPHRINE

Report of a Case

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Washington, D. C.

THE use of epinephrine in allergic conditions is widespread, yet the number of troublesome reactions reported are minimal.^{2, 3, 4, 6, 8, 9} It should be stated here that practically all of the reactions reported are merely exaggerated degrees of the normal pharmacological actions of this drug. This report of convulsions after epinephrine is given not to warn against the use of this valuable drug nor to present any rare phenomenon, but merely to illustrate that puzzling and complex reactions can arise from simple effects of a drug.

CASE HISTORY

M.H., a twenty-six-year-old white man, with a history of seasonal and perennial hay fever and asthma, was being treated with allergic extracts of house dust, ragweed, and plantain. The patient had been tolerating the treatment very well. During one of his visits he was noted to have had a flare-up of his symptoms following environmental exposure to greater amounts of the causative factors. He was given smaller amounts of his allergic extracts, and in addition was given 5 minims of 1/1000 epinephrine solution. In about ten minutes, the patient returned from the waiting room stating he felt as though he were going to have a convulsion, and as he was being placed on the bed, he developed a series of convulsions.

The seizures began about ten minutes after the injection and lasted for a total of thirty minutes. They consisted of intermittent, generalized, tonic and clonic convulsions, lasting thirty to ninety seconds, and recurring every two to four minutes. The convulsions resembled those of tetanus or strychnine poisoning. The patient was conscious throughout and was able to talk between his seizures, but during an attack he presented a picture of opisthotonos, with tonic and clonic spasms of all his muscles, the stronger muscle groups producing the characteristic effects. His skin was warm and flushed, and his only subjective complaints were a sense of "drawing" in his arms, legs, and face, and a "fear" sensation. During each attack he would weep and pant deeply. He was unable to control his crying or his respirations during the seizure, but between attacks he was able to co-operate in every way. There was no headache, no carpo-pedal spasm, no defecation or urination, and no injury to tongue, et cetera.

During the intervals between convulsions, physical examination and neurological examination were essentially negative. A summary of the pertinent factors in pulse, blood pressure, respirations, et cetera, is shown in Figure 1. After about thirty minutes, the convulsions gradually and spontaneously subsided, leaving the patient exhausted and tired. He was able to return home by himself after one hour, and by the next day he was entirely well.

FOLLOW-UP STUDIES

After the convulsions had subsided, our attention was directed to the investigation of the cause of the phenomenon. The first thing suspected was the dosage of the allergic extracts, but this was found to be correct

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and has been given to him since then without effect. The epinephrine solution was a 1/1000 solution in a rubber-stoppered multiple-dose vial. This solution has been used on several other individuals without any

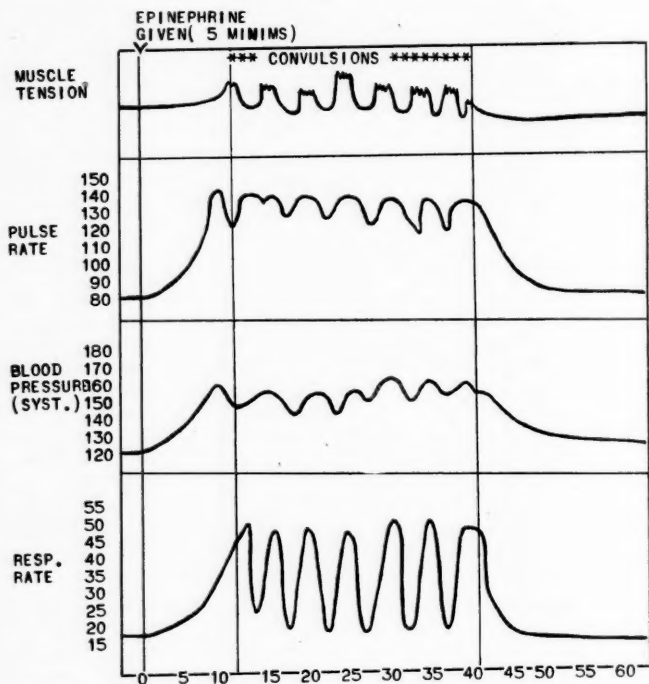


Fig. 1. Effect of epinephrine on the various physiological functions of the patient. Note in particular the prolonged effect on the respiratory system.

unusual effects. The possibility of intravenous injection of these solutions, or of other factors being significant was eliminated by subsequent demonstration that convulsive seizures could be reproduced in this individual by subcutaneous injections of 1/1000 epinephrine in amounts over 5 minims. It was noted that it was easier to produce a convulsion after he had taken a dose of ephedrine, and in view of the augmentative effect of ephedrine on the action of epinephrine,⁵ this seems quite logical. Since all studies seemed to indicate that neither the allergic extracts nor the epinephrine solution nor the methods of injection were at fault, our attention was next directed to the patient.

A careful and detailed history of the patient revealed no personal or family history of epilepsy. The patient subsequently revealed that he had suffered two previous attacks of convulsions after epinephrine. The first occurred after an injection of epinephrine for an attack of asthma,

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and the second after excessive self-dosage with a 1/100 solution of epinephrine in a nebulizer. These attacks were similar to the one described above. They subsided by themselves, and no studies were made to determine the cause of these seizures.

A careful physical examination was negative except for the presence of an asthmatic type of chest and an allergic nasal mucosa. There was no evidence of other associated diseases which could explain the sensitivity to epinephrine, e.g., hypertension, hyperthyroidism, pheochromocytoma, et cetera. Neuropsychiatric examination was negative except for a moderate anxiety state and mild vasomotor unbalance. All reflexes were normal, and Trousseau's and Chvostek's signs were negative. Electrical stimulation of his muscles revealed a normal threshold of reaction.

Laboratory studies were essentially normal in regard to blood picture, urine, blood sugar and glucose tolerance, calcium, phosphorus. The basal metabolism rate was normal, and x-ray studies of the skull, chest and abdomen were normal.

This condition seems to represent a transient, widespread involvement at the peripheral myoneural level rather than a central involvement, yet when the attack was over, there was no evidence of any disease. This could possibly be explained by a transient lowering of the threshold of irritability of the myoneural junction during the time of action of the epinephrine. While there have been some studies to indicate the direct action of epinephrine on the myoneural junction,⁷ there is reason to believe that the explanation is in reality very simple. One notes in Figure 1 that the pulse rate and blood pressure begin to return to a more normal level before the convulsion starts, but one also notes that the rate and depth of the respirations continue to increase until they merge into a spell of hyperventilation just before each of his convulsions. In short, the cause of the patient's convulsions is a variation of hyperventilation tetany.

A résumé of the process is as follows: the patient is a nervous, tense individual who is quite susceptible (when under the effect of ephedrine) to the stimulating effect of epinephrine on his central nervous system and especially on the respiratory center. This results in the increase of rate and depth of respirations and culminates in hyperventilation tetany which is manifested by convulsions.

It is of interest to note a report of the use of epinephrine in anxiety states where the "tension producing" effect of this drug was used to gradually "desensitize" the patient to the symptoms of his anxiety state by repeated and increasing doses of intravenous epinephrine.¹ There was no report of convulsions in these cases, although the author noted transient reactivation of those symptoms which made up the customary pattern of anxiety of the individual patient, e.g., palpitation, choking sensations, dyspnea, hyperventilation, et cetera.

(Continued on Page 210)

Department of Clinical Pathology and Laboratory Procedures

THE WELTMANN REACTION IN ALLERGIC RHINITIS

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Durham, North Carolina

THE Weltmann reaction as a laboratory diagnostic aid in allergic diseases has been discussed in this department recently, and the simple modification of Weltmann's technique has been described.^{1,2,5,6} In our studies it has seemed that the most important technical factor in assuring uniform and reliable results is to maintain a constant temperature of 100° C. for

TABLE I. WELTMANN COAGULATION REACTION IN ALLERGIC RHINITIS.

Weltmann Coagulation Band	1	2	3	4	4½	5	5½	6	6½	7	7½	8	9	Total Patients
Allergic rhinitis, uncomplicated						1		61	5	19	1			87
Allergic rhinitis with non-inflammatory disorders								6	2	7	1	1		17
Allergic rhinitis with inflammatory disorders				3	1	15	3	9						31

Total Number of Patients=135

the entire fifteen minutes required for boiling the serum-calcium-chloride dilutions. If the temperature is allowed to fall even 3° C., certain sera will give falsely low coagulation bands. Schweinburg and Evans⁸ report that buffered solutions of calcium chloride are preferable to simple dilutions, but in our studies pH of the solutions has not seemed to affect results provided a constant temperature of 100° C. is maintained.⁴

Weltmann reactions have been done on a series of 135 unselected patients with allergic rhinitis as the only allergic condition. Some of the patients have also had other diseases, and on the basis of the final clinical diagnosis the patients have been separated into three groups: (1) uncomplicated allergic rhinitis, (2) allergic rhinitis associated with inflammatory

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CLINICAL PATHOLOGY AND LABORATORY PROCEDURES

conditions, and (3) allergic rhinitis associated with noninflammatory conditions.

The coagulation bands for each of the three groups is shown in Table I and Figures 1 and 2. The patients with allergic rhinitis alone fall pri-

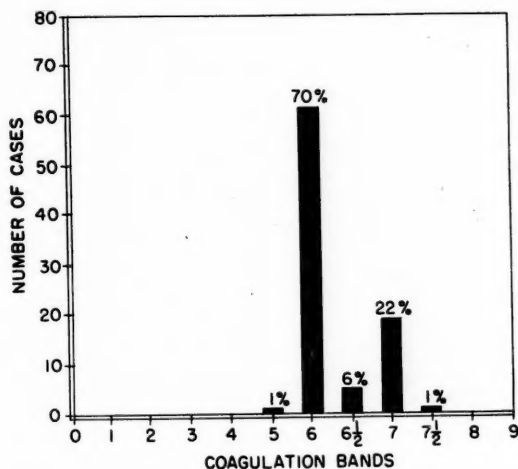


Fig. 1. Allergic rhinitis, uncomplicated.

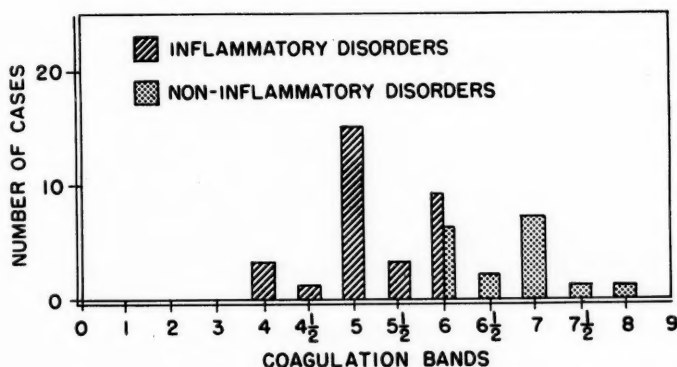


Fig. 2. Allergic rhinitis with complications.

marily into bands of 6 or 7. Those with inflammatory disorders are all less than 6, while those with noninflammatory conditions are from 6 to 8. Since many adults are included in this series, it is quite probable that mild and undiagnosed conditions of a fibrotic type are included among the patients classified as having allergic rhinitis alone, which may partially account for many of the values of 7 seen in Group 1. In studies done on children and young adults, one is impressed with the rarity with which

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TABLE II. ALLERGIC RHINITIS WITH INFLAMMATORY DISORDERS.

No. of Patients	Age	CB	Corrected Sed. Rate (mm./hr.)	White Blood Count	Associated Clinical Findings
15	10 - 55	4 - 6	1 - 43	4650 - 11,100	Acute and chronic sinusitis
10	5 - 32	4½ - 6	5 - 32	6500 - 13,150	Tonsillitis and adenoiditis
2	4 a 59	6	0 a 30	6950 a 10,000	Chronic bronchitis

TABLE III. ALLERGIC RHINITIS WITH NON-INFLAMMATORY DISORDERS.

No. of Patients	Age	CB	Corrected Sed. Rate (mm./hr.)	White Blood Count	Associated Clinical Findings
6	4 - 20	6 - 8	7 - 16	4200 - 9800	Lymphoid hyperplasia of pharynx
4	33 - 55	7	16 - 24	6550 - 11,200	Nasal polyps
3	49 - 58	6	10	4800 - 8700	Arteriosclerosis, general
2	36 a 41	6½ a 7	12	4750 a 5500	Chronic cystic mastitis
2	36 a 49	6 a 7½	24	8700 a 11,250	Arthritis

values over 6½ are encountered in healthy normal individuals, or in uncomplicated allergy.³ Weltmann⁸ and others consider the normal range for all ages as 6 to 7.

The Weltmann reaction, corrected sedimentation rate, white blood count and clinical findings are presented in Tables II and III for patients with complicated allergic rhinitis. It will be noted that white blood counts and sedimentation rates vary over approximately the same range for both the infectious and noninfectious types of complications. The Weltmann reactions, however, are predominantly below 6 in the inflammatory group and above 6 in the noninflammatory group, with a close correlation to the patients' clinical condition.

Taken in conjunction with other data, the Weltmann reaction, though nonspecific, is peculiarly well adapted for use in allergic rhinitis. Here the clinical problem is primarily not one of making the basic diagnosis, but of recognizing complications of an infectious nature. These secondary factors, mimicking allergic symptoms, or altered by previous chemotherapy or local treatment may greatly modify the management of any given case. A laboratory test such as the Weltmann reaction, which has a remarkably constant value in the majority of normal persons, calls attention for the need to search for other disease processes which may also be present, if it deviates significantly from the expected normal range.

(Continued on Page 218)

Editorial

The opinions expressed by the writers of editorials in the ANNALS do not necessarily represent the group opinion of the Board or of the College.

THE DOSE OF A DRUG

The recent appearance of a number of new drugs useful for the symptomatic treatment of allergic conditions has resulted as well in the publication of a large number of papers concerned with the symptomatic relief achieved by certain levels of dosage. The authors list the "average dose" given each patient.

The phrase "average dose" has an exact meaning as used in the field of pharmacology, signifying the dose which can be depended upon to elicit the typical pharmacological response in 50 per cent of the population selected for testing. In toxicological experiments in which lethal effects are being measured, it is abbreviated as LD50. The phrase cannot be used to define the mean between the largest and smallest doses administered. As stressed in a recent Conference on Therapy* the phrase is not to be taken as defining the dose which produces its full effect in almost all patients nor as the "minimal" or "safe" dose.

The authors of the Conference discuss two types of dosage plans, the cumulative and non-cumulative.

The former involves the administration of small doses repeated at such intervals as to cause a final tissue concentration sufficient to produce the therapeutic effect desired. It is necessary, of course, to know the interval required for the dose to reach its maximal effect. Since, for example, with morphine if such effects occur in thirty to forty-five minutes, no purpose can be achieved by more frequent administration.

The non-cumulative method requires the administration of a single therapeutically effective dose each given when the previous dose has been completely eliminated from the body. In order to know that no cumulative effects have occurred it is necessary to know the time of absorption, the duration of action, the speed of elimination, as well as the time required to reach such maximal results. For some drugs, as digitalis, cumulative action occurs for approximately 14-21 days while with quinidine it can be expected in four to five days.

As work progresses with Decapryn, Trimeton, Antistine, Hetramine, and other similar drugs, it would seem best that emphasis be given to the method by means of which the effective dosage level was obtained and what side effects, if any, were due to the single as compared to the cumulative dosage taken.

*Conference on Therapy. The Dose of a Drug. Am. J. Med., 2:296-308, 1947.

EDITORIAL

SEASONAL VARIATION IN DRUG EFFECTS

Physicians interested in the evaluation of drugs used in the treatment of patients presenting allergic symptoms are accustomed to take into consideration the effects of seasonal variations in responses due to the presence or absence of factors as varied as pollination, house dust, humidity, and marked frequency of barometric changes. So far there have been no studies on the effects of seasons as such, comparable to those studies done on animals.

Taking each quarter of the year as arbitrarily ending on March the thirty-first, June the thirtieth, September the thirtieth and December the thirty-first, it has been shown by Burn that in the standardization of digitalis using frogs only 81 per cent of the drug is required for the first quarter tests as compared to 152 per cent for the third quarter. Nedzel has reported that neoarsphenamine causes greater liver and kidney damage in the third quarter as compared to the second. In rabbits sensitivity to insulin is most marked in the third quarter and resistance in the fourth, while neoarsphenamine is more toxic in the fourth quarter than in the third.

Rats are said to be more resistant to the convulsive action of insulin during the summer months but more resistant to the action of follicular hormone during the last and first quarters of the year. Caffeine increases metabolic rate and sodium excretion in the last and first quarters but decreases these in the second and third. Testosterone causes a greater rate of growth in the winter, as compared to the summer months.

Munch, Sloane, and Latven suggest that the variation of the effects of drugs in animals may be minimized by simultaneous assays of a uniform reference standard. Although it is difficult, if not impossible, to have exact evaluations of this type in patients who are not normal as are the animals used for assay purposes, nevertheless, the inclusion in clinical reports of the dates between which the medicines tested were used might bring to light such changes and response as may be due to season alone. When information of this type is reported as part of the data, it may help explain differences in results not at present explicable.

THE 1949 ANNUAL MEETING—ACA

The 1949 annual meeting of the American College of Allergists will be held at the Palmer House, Chicago, April 15-17. The Program Committee anticipates that a large number of scientific papers will be offered. Those who wish to read a paper should submit the manuscript or a 250-word summary to the Program Chairman, Dr. John H. Mitchell, 695 Bryden Road, Columbus, Ohio. All manuscripts will be carefully considered by the committee as a whole and final decisions will be made October 1.

Also those who wish a booth for a scientific exhibit, are requested to write to Dr. Leon Unger, 185 North Wabash Avenue, Chicago 1, Illinois. Those manufacturers desiring industrial exhibits should write to the Secretary, 423 La Salle Medical Building, Minneapolis 2, Minnesota.

Progress in Allergy

BRONCHIAL ASTHMA (IV)

Critical Review of Literature

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Chicago, Illinois

(Continued from the January-February issue.)

THERAPY WITH OTHER DRUGS

Inhalation of other drugs has been tried. Oxygen and helium have been used for years and are indicated when cyanosis is present. In uncomplicated asthma they are not too effective. Doll⁹¹ points out that helium is not likely to be of service in asthma in which the obstruction is in the smallest passages; on the other hand, if obstruction exists in the larger passages, e.g., larynx, there are good theoretical reasons for expecting relief with helium. Rubin²⁰⁶ has a good paper on oxygen therapy in asthma. Obstruction, he states, is due to bronchospasm, edema of the mucosa, and interference with pulmonary circulation. In adults or adolescents with asthma, he gives oxygen for seven days, starting with a concentration of sixty per cent the first two days, at 12 liters per minute, 50 per cent the third day, reducing to 35 per cent by the seventh day.

Inhalation of Aleudrin (isopropyl epinephrine) gave excellent results, says Charlier.⁶³ It led to improvement in twenty-three of twenty-seven asthmatic patients, whereas only six of these twenty-seven were benefited by vitamin therapy. [Other reports with Aleudrin are coming in; this drug will bear watching.]

Butaneprine (Ethyl-Nor-Epinephrine) has now been compared with epinephrine by inhalation, states Hartman.¹⁵⁸ In uncomplicated extrinsic asthma, a 2 per cent solution of the new drug is almost as effective as 1 per cent epinephrine, their bronchodilator powers being equal. But if infection is also present, epinephrine is much more effective, presumably because of its additional vasoconstrictor action. The new drug is better because it has less side effects, both local and systemic. The two drugs were tried in fourteen cases of asthma complicated by infection and in twenty-eight cases of uncomplicated extrinsic asthma.

Butaneprine has also been used parenterally by a number of other workers. Bubert and Doenges⁸³ injected 1 to 4 mg. intramuscularly in forty asthmatics. In sixty-six attacks, 100 per cent relief was obtained in twenty-two cases, 75 per cent relief in eighteen, 50 per cent in twelve, with increased vital capacity after injections. In 21 severe attacks, 1 to 10 mg. of the drug (average 2.4 mg.) was injected intravenously. Systolic blood pressure fell an average of 16 mm. mercury and diastolic 8 mm. Reduction in blood pressure began immediately and lasted about thirty minutes. Nervousness, fainting and generalized erythema occurred in some cases, but some patients preferred the drug to epinephrine because of its "freedom from pressor effects and central nervous system stimulation." The University of Maryland Allergy Clinic has been using the drug freely for eighteen months.

Results of a questionnaire²⁸³ regarding Butaneprine indicates a lack of agreement as to its efficiency, as compared with that of epinephrine. Most answers seemed lukewarm, e.g., Braden, A. Ford Wolf, Bartlett, Green, and Prince; Glaser likes it in children, Wolf in elderly asthmatics, especially if hypertension is present. Foland and V. Cohen use it a great deal. [We have not tried it.]

Aminophylline continues to be the "one-two" drug in the treatment of bronchial asthma. Epinephrine ranks first in children and in some adults, but in our experience, especially in adults, aminophylline intravenously (intermittently or continuously) gives quicker and more complete relief. The dosage in the home or office should be 0.25 gm., using a 10 c.c. syringe. In the hospital it should also be given in a liter of 5 per cent glucose, using 0.50 gm., repeated daily, as necessary, at 60 drops per minute. If asthma persists, the continuous method should be used, as reported by Goodall and Unger.¹⁴⁵ Status asthmaticus was completely or partially eliminated in nine of ten patients; relapse may or may not occur when the procedure is dis-

PROGRESS IN ALLERGY

continued. Daily dosage consists of up to 2 or even 3 gm. of aminophylline dissolved in 2,000 c.c. of 5 per cent glucose or normal saline solution, alternating; the rate is 28 drops per minute. The larger amounts of the drug are used initially and gradually reduced as symptoms subside. There is no danger at the above rate. [Since this article was published, we have continued this procedure and have been able to relieve many attacks of severe status asthmaticus].

Turiaf and Bourel³⁴⁸ also obtained excellent results with theophylline and theophylline ethylenediamine (aminophylline). One intravenous injection of 0.25 gm. in the morning and one in the evening, and one 0.35 gm. suppository at noon brought radical relief of dyspnea in five to ten minutes after the injection and in fifteen to twenty minutes after the suppository. This treatment was excellent in 150 (of 181) asthmatic patients, 108 of whom had paroxysmal, thirty-eight continuous, and four effort dyspnea. There were no untoward symptoms. They suggest that the good results may be partly due to its effect on the vasomotor apparatus of the bronchial epithelial lining. Jacquelin and his associates¹⁸² are undecided as to the mode of action of aminophylline.

Prigal, Fuchs and Schulman²⁶⁷ introduced a rectal suppository (Aminets) for use in asthma. The adult size contains 0.5 gm. aminophylline and 0.1 gm. pentobarbital sodium; the child's size contains 50 per cent dosage of each. The combination is better than aminophylline alone. Results: in twenty-five asthmatic patients suppositories containing sodium pentobarbital alone led to improvement in only one. In forty-seven patients given aminophylline alone, there was relief in thirty-eight (80.8 per cent) in from ten to sixty minutes. In forty-seven patients given Aminets: relief occurred in forty-four (93.5 per cent) in five to thirty minutes. The same patients were used in all tests, and the majority preferred Aminets because the response came more quickly and lasted longer. (Intravenous aminophylline was necessary in the severe asthmatics.) In the prevention of attacks, Aminets also was better than aminophylline: 93.5 per cent to 55.5 per cent. Aminets may cause some itching, burning and cramps; there was diarrhea in two cases. Aminophylline suppositories also aided asthmatic patients of Friedenber¹²³.

Lee²¹⁰ rightly points out that abscesses can follow intramuscular injections of aminophylline, and when it is injected intravenously too rapidly, or in too large amounts it has produced profound shock, necessitating intravenous fluids and cardio-respiratory stimulation. Wyrens³⁷⁹ states that aminophylline can cause fatality, referring to Merrill's article (J.A.M.A., 123:1115, 1943). [We have shown, I believe, that Merrill's patients had cardiac disease, not bronchial asthma³⁵¹].

Thompson and Warren³⁴² report that the acute toxicities of butaphyllamine and aminophylline were similar on intravenous administration to rabbits and ingestion in mice. In dogs, the daily administration of either compound for twelve weeks intravenously or orally, in doses of 20 mg. per kg., did not produce toxic effects. The body weights and the blood of the dogs were not altered, and there were no pathologic effects. No toxic changes occurred in rats who were fed these drugs as much as 34 mg. per kg. per day for as long as sixty days. Breysbraak and Greenspun¹⁶ found that the prothrombin time in a small series of human subjects was unaltered after large doses of aminophylline orally or intravenously.

[We can conclude, then, that aminophylline is a very safe drug in bronchial asthma, provided, of course, it is injected slowly and in dosages known to be safe. Reactions are likely if the speed of injection is too rapid or if the dosage is out of line.]

Prigal and his associates²⁶⁸ have introduced aerosol aminophylline. In forty adult asthmatics, inhalation through their steam generator-aerosolizer gave more or less relief in 80 per cent. In five patients (12.5 per cent), severe asthma failed to respond to intravenous aminophylline but was relieved by aerosol; the reverse was true in some cases, and in some there was no response to either method. [Their figures as to efficiency and vital capacity are hard to understand because they compared results from 0.125 gm. intravenously with 0.25 to 0.50 gm. by inhalation; one rarely gives less than 0.25 gm. by vein. Nevertheless, the method is very promising.]

Epinephrine rightly continues to be the other "one-two" drug in therapy of bronchial asthma, by subcutaneous, intramuscular, and inhalation routes, occasionally by vein. Surinych Oller³³¹ urges conditioning of this drug, as by mixing with oil, to slow its action. Ratner's four-year-old patient²⁷⁹ received 1.0 c.c. Adrenalin in oil (Parke, Davis) and developed over a three-month period an induration which reached a 7 cm. diameter. The oleoma was removed, and fat globules were seen under the microscope. The boy was not sensitive to the peanut oil used as a vehicle.

Two cases illustrate overdose of epinephrine. Horwitz's twenty-one-year-old male¹⁷² had urticaria; by error, he received 7.0 c.c. of a 1:1,000 solution intra-

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muscularly. He was put to bed and an ice pack applied, and he was given 0.4 gm. sodium amyltal orally. Only a slight headache occurred; his maximum pulse rate was 128; his blood pressure rose to 220/96. The electrocardiogram was normal except for tachycardia, and all symptoms and signs subsided in five hours. In the other patient, reported by McGinty and Baer,²³³ believed to have malaria, aged twenty-nine, male, another error occurred: 5 c.c. of 1:1,000 epinephrine was injected intramuscularly. Immediate precordial distress occurred and the pulse became imperceptible. In five minutes the blood pressure was 120/80 and vomiting occurred; in thirty minutes the pulse was 140, the pressure 199/60. He was hospitalized twenty-three hours later because of constricting chest pain, dyspnea, and headache, with 101° F., pulse 105, and pressure 94/60. Electrocardiographic changes suggesting infarction persisted for a month, along with left temporal headache, then recovery.

Herxheimer¹⁶² treated sixty-five asthmatic patients with and without ephedrine and his best results came when he gave the drug for three to four days, then a free interval of three to four days, then ephedrine again. Small doses gave good results in each of fourteen patients who had mild asthma. In a second group (fourteen severe extrinsic asthmatics and thirty-seven emphysematous patients with or without a preceding history of asthma), the results from ephedrine varied: five responded well to less than 1 grain three times daily; three were hyperresponsive to very small doses; twenty-eight needed ephedrine doses as high as $3\frac{1}{2}$ grains three times daily before relief occurred; and eight were refractory to even as much as 3 to 4 grains three times daily. Effectual dosages caused an average increase of 518 c.c. in vital capacity. Some patients who seemed toxic the first day or two after taking ephedrine were later able to take it successfully. [Note that his dosages are much higher than those customarily given in this country. We suggest trial of large amounts where possible.]

Some still give *morphine* for asthmatic attacks, but, happily, more and more men realize that it prevents expectoration of mucus and that it slows the rate of respiration. Bowen⁴⁰ states: "On rare occasions exhaustion of the patient may, seemingly, justify morphine, and if it is used, the dosage should be very small. Morphine should never be used in children." This statement does not satisfy Homan¹⁷¹ who says, "The use of morphine in an exhausted asthmatic is very likely to usher the patient quietly into the next world." Mistry, from Bombay,²⁴³ advocates subcutaneous injections of 1 minim every five minutes for ten doses of a mixture containing $\frac{1}{4}$ grain morphine, 1/100 gr. atropine, and 10 minims of 1:1,000 epinephrine. Laird,²⁰⁵ in a study of 126 asthmatics admitted to St. Mary's Hospital (Duluth, Minn.) in 1944 and 1945, found that 11.9 per cent of the patients had had injections of morphine before admission, a sad state of affairs.

Demerol (Meperidine hydrochloride) is being used too much in asthma. It does not depress the cough reflex to the extent morphine does, but in our experience it is of limited value in asthma. Sedation with seconal or similar hypnotic seems preferable. When used, it is best to give 50 mg. doses instead of 100, as suggested by Barach.²³ Patients with primary Demerol addiction have recently been admitted to the United States Public Health Service Hospital.⁸⁷ The drug has been subject to the provisions of the Federal Narcotic Law since July 1, 1944. Caution is urged. Each of three addicts admitted found it necessary to increase dosage to obtain the desired pleasure, and one took as much as 4,000 mg. a day in 500 mg. doses. Polonio²⁶⁴ says that in 1944 he and Barabona collected seventeen cases of addiction with Demerol from the literature, with three deaths, and added six cases of their own, with one death. Since then, he has observed nine more cases of addiction, with one death. The drug may be even more dangerous in the long run than morphine.

Hycodan (Dihydrocodeinone) has been tried for three years by Stein and Lowy³²⁶ for the treatment of cough. Depression of respiration is at least as great as from morphine though the new drug is less nauseating and constipating. Since bronchospasm is not relieved, the drug seems useless in bronchial asthma. In nine patients studied intensively, both codeine and Hycodan decreased sputum output; in six of these the cough was better controlled by Hycodan.

E. A. Brown injected 5 per cent *ethyl alcohol* solution in five per cent glucose-saline, with or without 0.3 to 1.0 c.c. epinephrine 1:1,000, and relieved five of six patients who had severe bronchial asthma.⁵⁰ The injections were given intravenously at the rate of 80 to 100 drops per minute. There were no ill effects. Later, Brown and Gillaspie⁵¹ report even better results by giving 100 to 120 drops per minute, later slowing to 60 to 80. Brown used it in seventy-two different patients and Gillaspie in about twenty. The patients relax quickly, breathe deeply, are flushed, and fall asleep. If sleep does not occur, the solution is being injected too slowly. This method

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has apparently not been tried in children. [We have tried it in a few patients, with fairly good results in one or two, but we probably injected the alcohol too slowly.]

Klaarenbeek¹⁹⁸ obtained favorable results in young asthmatic patients by series of injections of a copper preparation, beginning twice weekly, later once or twice a month. Spitzer³²⁴ injected 5 c.c. of *Coramin* intravenously with prompt relief of severe asthma in fifteen patients. The patient's face becomes dark red, there is tingling of the extremities, the pulse rate falls from perhaps 150 to 90, and the sonorous and sibilant râles disappear, all within one to two minutes, followed by copious expectoration. This good effect lasts about twelve hours (average). One may inject a second 5 c.c. intravenously within five minutes, if necessary, with no toxicity. *Coramin* has been used in some patients for months without habituation, and each injection works just as promptly and effectively as the first, according to Spitzer.

Novocaine and *procaine* are also used in the treatment of asthma. Durieu and his associates⁹⁸ gave daily intravenous injections of from 5 to 20 c.c. of a one per cent solution of procaine hydrochloride without epinephrine to twenty-five patients. In paroxysmal asthma, lasting improvement is obtained in half the cases and temporary improvement in another 30 per cent. In chronic asthma with emphysema and bronchitis, only 30 per cent show temporary improvement. The drug is useless for dyspnea of pulmonary sclerosis. Phenobarbital by mouth improves the tolerance for procaine.

Jacquelin and his co-workers¹⁸³ have been able to increase the vital capacity and in some cases to double it by intravenous injections of novocaine. Novocaine³⁴⁵ was first recommended for the treatment of bronchial asthma by Dos Ghali and his co-workers (*Presse méd. belg.*, 11, 1941); theoretical reasons for success are suggested. Several other men have used it, including Durieu in twenty-five patients, with good results. [Warning: drugs of this group may be dangerous.]

Treuherz³⁴⁶ obtained excellent results in twenty-three asthmatics by the oral administration of protein preparations ST 1, 2, 3, a new composition of albumine said to possess both anti-allergic and anti-infectious properties. Edmondson¹⁰² claims complete recovery in ten cases of hay fever and asthma by intranasal application of "Agcuzin" compounds, manufactured by the Allergy Clinic in Amarillo, Texas.

"Agcuzin," according to information obtained by the Council on Pharmacy and Chemistry of the American Medical Association, is a later name for the asthma and hay fever treatment of Dr. E. Edmondson, which used to be called "Metapollen." In a report of the Council on Pharmacy and Chemistry published in the *J.A.M.A.* on February 18, 1933, they stated that Metapollen was not acceptable for *N.N.R.* because "(1) no satisfactory formula had been furnished by the manufacturer, (2) the claims of special therapeutic usefulness were not warranted by the evidence, and (3) the composition is unscientific."

Although the Edmondson treatment has apparently undergone some change during the past fifteen years, it seems to be essentially a series of solutions of astringent drugs in several different concentrations. According to a report by Dr. Edmondson (*Texas State Journal Med.*, January, 1944) "the Edmondson formula is propenyl-tri-hydroxide of anhydrous cupric and zinc sulphates and colloidal silver solutions." One wonders whether this vague but impressive terminology may not have been intended to hide the simple fact that the preparation is an aqueous solution containing extremely small amounts of glycerin, copper sulfate, zinc sulfate and silver nitrate. All three of these salts are mainly astringent and caustic, and if applied to the nasal mucous membrane, would be expected to shrink the mucosa through precipitation and destruction of the protein. On the basis of the known actions of the ingredients, it would appear likely that this preparation would do more harm than good. It certainly would not affect the underlying basis for the allergic state. The presently available reports of Dr. Edmondson provide no data which would invalidate the conclusions of the Council's report of 1933.

Urinary protease is apparently still being used, with success as regards dermatitis and ocular damage in an asthmatic woman who also had these two conditions (Rhoads²⁸⁴).

Anthallan,¹³ made by Nepera Chemical Co., was submitted for trial to seven members of the American Academy of Allergy. A total of 185 cases were used. Results: in ninety-eight cases of ragweed hay fever: 3 per cent benefit; in twenty-one cases of perennial rhinitis: 4 per cent; in seven atopic dermatitis: 14 per cent; in fourteen cases of bronchial asthma: no benefit at all. The committee concluded that the drug was without value.

Ethylene disulfonate was studied by Brenner and Stoesser⁴⁵ in ten hospitalized

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chronic asthmatics. The drug proved almost valueless (one good result, two fair, seven poor). In five others, triple distilled water was used, with equal results (one good, two fair, two poor). The Council on Pharmacy and Chemistry of the American Medical Association¹⁰⁷ examined this drug put out as "Allergosil" by the Spicer-Gerhart Co. It could not distinguish it from distilled water, and brands it as without therapeutic value and unacceptable for *New and Nonofficial Remedies*.

Boyd and his associates⁴² showed, in guinea pigs, that volatile oils cause an increased flow of fluids from the respiratory tract. Oil of anise was most effective, followed by oils of turpentine, pine, lemon, and eucalyptus, and by terpin hydrate and terebren. Compound tincture of benzoin had no expectorant action. A mixture (aminophylline, potassium citrate, wine of ipecac, chloroform, in syrup) increased the volume of respiratory tract fluid in four of six species of animals and in seventy-two per cent of human beings, but there is no synergistic action by combining these expectorants.

An asthmatic without previous urinary trouble was given a total of thirteen tablets, each containing 0.50 gm. sulfadiazine, in divided doses. From the first dose, states Finegold,¹¹³ she did not void; vomiting followed, and intravenous fluids were given. A urologist could not catheterize the ureters. On the fifth day of anuria, she was admitted to the author's hospital with acute asthma, cyanosis, dehydration, fever, tachycardia, rapid respiration and blood pressure 150/85. Cystoscopy revealed inflammation of the bladder mucosa plus grayish gelatinous material oozing from both ureteral orifices. The obstruction was thought due to edema; no crystals were found in the wash water. An intravenous drip containing 5 per cent glucose, 4 c.c. 1:1,000 epinephrine and 0.50 gm. aminophylline, ended the anuria and relieved the asthma. The intravenous treatment was repeated when asthma and anuria recurred, and the patient left the hospital on the twentieth day with normal urination and no wheezing.

There is the usual interest in the treatment of status asthmaticus, though there is nothing very new except for the use of aminophylline by continuous drip and the rapid injection of alcohol—both already mentioned. Barach²⁸ emphasizes the need for continued search for allergens, the use of oxygen, Demerol, phenobarbital, atropine, helium, 50 per cent and five per cent glucose, rectal and generalized anesthesia with ether, bronchoscopic aspiration, fever therapy, manual elevation of the diaphragm (which increases vital capacity 200 to 1,000 c.c.), and the inhalation of antibiotics into lungs and sinuses when infection is present. Carrier and his co-workers⁵⁸ urge hospitalization of severely ill asthmatics and specify steps to make those rooms dust-free. [Why not have rooms available at all times, with air filters or air conditioning, and with rubber bedding? We have been able to give quick service to many such patients with our twelve beds in our "asthma" rooms at Wesley Memorial Hospital.] They favor the BLB oxygen mask and often use 80 per cent helium and 20 per cent oxygen, plus intravenous injections of 10 or 20 per cent dextrose solution containing 0.25 gm. aminophylline. They also use Coramine (nikethamide) if respiratory failure seems imminent.

Sutherland,³⁸⁴ from Australia, follows pretty much the well-known routine. He may use morphine in early stages in vigorous patients, but prefers Demerol.

H. Miller has an excellent outline on the treatment of bronchial asthma (and hay fever) for the house staff of his hospital.²⁴¹ He especially warns about the danger of morphine and the risk of "aspirin asthma" in some patients. One should look for complications or wrong diagnosis if the usual treatment is ineffective. He states that "cor pulmonale never occurs in uncomplicated bronchial asthma."

MISCELLANEOUS MEASURES IN THERAPY

Waldrott³⁶⁵ cautions against after-attack neglect. To avoid chronic invalidism, the patient should have carefully gauged light exercise; gradual exposure to his offending allergens; high caloric diet when patient is underweight; increase of tolerance to cold by gradually increasing exposure; and gradual decrease in the use of drugs, especially epinephrine sprays. He stresses the great value in severe attacks of bronchoscopic aspiration followed by lavage of the bronchial tree with saline solution, a life-saving procedure and always successful. [He is a bit casual about caution in avoiding house dust and pollens though he does say "there can be no objection to advocating cleanliness in a home, nor to using a rubber cover on the mattress and on the feather pillows." Such loose advice from a leading allergist can only lead to carelessness in the management of asthmatic patients. We do not subscribe to this philosophy; we make every effort to have our patients continue avoidance of inhalant allergens.]

Banyai²⁰ favors carbon dioxide to eliminate inflammatory products accumulated in

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the bronchopulmonary airways. Inhalation of 5 to 10 per cent carbon dioxide and 90 to 95 per cent oxygen is simple, safe, and superior in results, and definitely indicated for strenuous exhaustive nonproductive cough, dyspnea, bronchiectasis, or fluid-filled cavities communicating with a large bronchus. Carbon dioxide may be cautiously used in cardiac decompensation, but should not be used in pulmonary hemorrhage, severe emphysema, acute pleurisy, pleural effusions, hypertension, and a few other conditions. CO₂ and O₂ relieved cough in forty patients with previously uncontrolled cough and dyspnea. Banyai describes the usefulness of cough and its mechanism and physiology, but long-continued cough may cause emphysema. If the cough is useless and inadequate (tussic insufficiency), exhaustion may occur with stagnation of material in the bronchi, a major factor in producing bronchiectasis. Prolonged cough may also cause headache, pulmonary hemorrhage, spontaneous pneumothorax, and fractured ribs.

Treatment of "climatic" asthma is discussed by Surinyach Oller of Spain.³³² He stresses differences in environment of a patient as regards his room, his place of work, and the city in which he lives. The cities are the worst, he states.

Godlowski¹⁴² gave *insulin shock* therapy and completely relieved symptoms in seven of eight patients with allergic asthma. Three patients with nonallergic asthma did not respond. Success is probably due to stimulation of the adrenal medulla with resultant increased production and dissipation of epinephrine. Eight patients of Valis³³⁴ were also completely relieved of their asthmatic symptoms by insulin shock treatment; during the shock there was a temporary elevation of systolic and diastolic blood pressures, independent of variations in glycemia.

Pneumoperitoneum has been advanced for the treatment of bronchial asthma; the injected air elevates the depressed diaphragm. It may also have a reflex and nervous effect, says Taraglio,³³⁸ who injected air into seventeen asthmatic patients, twenty-five to fifty-eight years old. In four patients who had essential bronchial asthma, relief of symptoms occurred after three to four injections. In thirteen other patients in whom asthma was complicated by tuberculosis or silicosis or both, the wheezing and dyspnea disappeared in four patients within twenty days, and in seven others within sixty days.

Pneumoperitoneum has also been used successfully in three cases by Calvo, with repeated injections of from 300 to 900 c.c. of oxygen.⁵⁴ Since such injections displace the heart, Garcio Ortiz and Lopez Arribas¹³³ took electrocardiograms and found only mild temporary changes, e.g., inversion of the T wave.

Adams obtained good results in two cases of chronic asthma by a combination of psychotherapy ("pep" talks), stopping of all foods, and administration of sixteen tablespoonfuls of M. R. Thompson's Protein Hydrolyzate dissolved in a quart of boiling water, with addition of six to seven spoons of sugar—this mixture given all through the day. B-complex and multiple vitamins were added, and this regime was kept up for two weeks.³ Goodman¹⁴⁷ added aminoacids (½ ounce dry powdered Hydramin after each meal) to the diet of twenty-one asthmatic children living in the National Home for Jewish Children. After twelve weeks the average gain in weight and height far exceeded that of a control group of forty-eight asthmatic children. Alcaide and Garceron¹⁰ stress thiamine hydrochloride in asthma. Good results were obtained by daily intravenous injections in 100 mg. dosage (three cases).

Khellin seed extract (from Ammi Visnaga: Arabic Khella, which grows wild in the Eastern Mediterranean regions) has been used by the local population since ancient times as an antispasmodic in renal colic. It causes conspicuous and prolonged relaxation of smooth muscle, especially in the ureters. Anrep and his associates¹⁵ injected 200 to 300 mg. of khellin (visamin) intramuscularly. Forty-one of forty-five patients with severe bronchial asthma obtained complete and prolonged relief after one injection; in three cases a second injection was necessary. The action of khellin is not as prompt as that of epinephrine, but it is more lasting and vital capacity is increased 600 to 1,000 c.c. The drug relieved some asthmatics in whom both epinephrine and aminophylline had failed; no deaths occurred, and side effects were few and mild.

Sulfurated water has been used for asthma by Gasbarrini and Farnetti,¹³⁴ and Wilson³⁷² writes about the osteopathic treatment of asthma; besides manipulations, he purges patients to begin with, then adds one food at a time, uses breathing exercises, and has patients avoid inhalant materials.

Lumbar puncture with removal of a few c.c. of spinal fluid led to general improvement in eight severe asthmatic patients of Jonuleit.¹⁹⁰ Vital capacity was increased. The mechanism is unknown. Surgical blocking or resection of the sympathetic and sometimes of the plexus pulmonalis posterior of the vagus often is effective and lifesaving in severe bronchial asthma, say Hansen and Smidt.¹⁵⁴ Albanese⁹ has

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treated over 300 cases of bronchial asthma over a period of nine years, with a total of 4,000 to 5,000 anesthetic blocks. The benefit in bronchial asthma with blocks and resections of the vegetative nervous system at the level of the cervico-thoracic sector showed that in 100 patients, 80 to 85 per cent were improved or "cured." He describes in detail his various operative procedures. Complications can occur.

PSYCHIATRIC ASPECTS IN ASTHMA

The psychic aspects of bronchial asthma have been hotly debated for many years. At the June meeting (1946) of the American College of Allergists, an excellent symposium was held, under the direction of Abramson. Talks were given by both allergists and psychiatrists, and the great amount of agreement between the two groups was most satisfactory. Both agreed that psychiatric influences are very important, yet in themselves are not the cause of true bronchial asthma.

Mitchell and Curran²⁴⁴ outline a method of approach to psychosomatic problems in allergy. They realize, as do all of us, that one group of allergic patients follows rather strictly the allergic pattern; the other group is markedly influenced by functional stimuli. This latter group has multiple complaints, perennial, and with recurrence for periods of weeks, months or years, often with unexplained intervening periods of remission. In this group many other symptoms are common, e.g., insomnia, fatigue, and nervousness. The authors have developed "a predictable, teachable technique which has come to be known as 'nondirective psychotherapy,'" and is based on the work of Rogers, Curran, and others. The patient's history is not taken; rather, the patient is made to feel at ease, and is permitted to talk about himself in any way and in any order that he wishes. Direct questions are usually avoided. This unburdening is very informative and in itself frequently is amazingly helpful in treatment. Space does not permit a full report of this paper nor that of Mitchell, Curran and Myers.²⁴⁵ The reader is urged to study these two articles which represent a distinct advance in the therapy of some cases of asthma and other allergic conditions.

Henderson¹⁶⁰ discusses several cases of asthma and concludes: "one cannot too emphatically repudiate the misleading suggestion that bronchial asthma should be considered as a psychical disorder. I believe that it should be conceived of primarily as an organic disease based on disturbed respiratory physiology—the result of allergic influences, in which psychic and emotional factors may indeed be important in precipitating, modifying or inhibiting attacks in patients already the subjects of asthma. . . . There probably are some patients who consciously or unconsciously utilize their disease to excuse their deficiencies, and even to achieve their ends." As regards children, Henderson wisely suggests that "a little healthy neglect may even be preferable to oversolicitude." [This is in line with Peshkin's ideas about "parentectomy."]

Dees⁸⁵ also finds, in allergic children, that psychiatric influences are important, and often play a major role. She has three interesting case reports, and suggests that in many children with asthma and eczema an abnormal electroencephalogram becomes normal with improvement of the allergic condition. In discussing this paper, Arena expresses the point of view favored by most pediatric allergists: many of these behavior problems are secondary to the stress and strain brought on by their allergic states, and are not primary. Lowenbach added to the discussion that one should not too readily seek assistance of a psychiatrist in children with allergy. Every effort should be made to solve the problem from the point of view of the allergist.

Campbell⁵⁵ blasts the "unscientific approach of freudian psychoanalysis to problems of so-called functional disorders." Psychosomatic medicine is a definite entity but should not be taught by psychiatrists except as it relates to pure psychic conditions. "A course in psychosomatic medicine given to medical students should be one supervised by the surgeons, internists, allergists, dermatologists, and other physicians with the aim of pointing out to students the fact that environmental influences of a personal, social, religious, or otherwise designated character, do produce autonomic nervous system and intellectual reactions and other symptoms. But, the freudian, stekelian, jungian, rankian, adlerian,orneyian, radioian, kardinerian, meningerian, deutchian, kubian, and other fantasies as explanations of emotional effects upon human stability should not be taught as amounting to anything more than peculiar theories expounded by certain psychiatrists." Campbell says that asthma is supposedly a "stifled cry," symbolically bemoaning separation in the superintensive mother attachment. Such a theory, he says, is a "travesty upon scientific accomplishment."

Other recent papers on psychic influences in asthma are those of Kyer,²⁰⁴ written from the psychiatrist's viewpoint; Billings³¹—a study of seventeen cases of "psycho-

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genic" asthma, in which good results from "psychic" management occurred in six; Doyle,⁶⁵ who cleared asthma in a thirteen-year-old girl by removing oversolicitude on the part of the parents and jealousy toward a sister; S. Cohen,⁷² who interrogated two female asthmatics under sodium amytal hypnosis, and learned of emotional disturbances—when these were removed, asthmatic symptoms were greatly lessened; and Swanton,³³⁵ in which allergic symptoms "might" represent an inherited autonomic nervous system stigma. Cobb,⁶⁹ in a discussion of psychiatric problems at the Massachusetts General Hospital, notes three cases of bronchial asthma but omits all mention of allergy.

Kerman¹⁹⁵ reports two cases in which a previous asthma disappeared, but symptoms of affective psychosis occurred. Electric shock treatment led to mental improvement, but, coincidentally, the asthma returned; no change in exposure to allergens could be found. In two other cases, both severe and associated with extrinsic allergens, a series of six electroshock treatments in each led to marked increase of symptoms both emotional and asthmatic; Cohen and Holbrook,⁷³ therefore, believe that electroshock treatment is contraindicated in bronchial asthma.

ENDOCRINE INFLUENCES

Kogan,²⁰¹ from Moscow, reviews the literature on the relationship between endocrines and bronchial asthma. In seventy-two cases of asthma in women, eighteen had late appearance of menstruation, thirteen dysmenorrhea, two early menopause, nineteen more frequent and more severe attacks of asthma during periods, and nine had their first attacks with their first menstruation. In six patients asthma was increased during pregnancy, and these had extended freedom from asthma after delivery. In addition, four asthmatic patients were improved after thyroid disturbances were eliminated. Derbes and Soderman⁸⁹ conclude that (a) bronchial asthma may improve, disappear or be worse during pregnancy; (b) emptying of the uterus may lead to improvement in the asthma or at least duplicate the pre-pregnant condition, but abortion is rarely indicated.

Ravina and his co-workers²⁷⁵ discuss a pregnant woman with severe asthma; progesterone was given on the first day, with improvement on the third day. On the seventh day she received 60 mg. Lutein and her asthma disappeared. Injections were continued throughout pregnancy. After a normal delivery, smaller doses of 5 mg. every five days were given and the patient was still well eight months later. Six asthmatics who also had hyperthyroidism were given thiouracil ("tiourea") with complete cessation of attacks of asthma in five, according to Matas Pons.²²⁹

THE NOSE AND NASAL SINUSES AS RELATED TO ASTHMA

Operative procedures in the nose and nasal sinuses in asthma and perennial rhinitis and sinusitis are certainly diminishing, for which much praise. Most nose and throat specialists are now aware of allergy, some more than others. Many now come forward and condemn the recent orgy of nasal and sinus surgery. Van Alyea, a specialist in this field, studied sections of tissues removed from eighty-two patients; no membrane was so diseased as to be considered beyond the hope of repair. Eosinophils were found in most of the sections, "indicating that allergy is a dominant factor in maintenance of chronic sinus disease." He pleads for conservatism in the treatment of chronic maxillary sinusitis.³⁵⁵ Hill¹⁶⁷ echoes these statements in his review of progress in otolaryngology. Of allergy he says, "The allergist has come into his own as a full-fledged specialist and, if given the chance, can prove a beneficent influence on the over-zealous rhinological operator. It is still appalling to see the number of cases in which radical surgery is advised without any consideration of the possibility of allergy. Careful histories and repeated nasal smears will avoid many pitfalls."

Woodward³⁷⁵ pleads for co-operation between the rhinologist and allergist. After outlining various methods of diagnosis and treatment, including surgery, he concludes: (a) one should not condemn all sinus surgery in asthma; some procedures may give excellent results, others may be ill-advised; (b) "one should not expect to cure asthma by surgery, but rather to clear up a condition which should be eliminated regardless of asthma, for, by so doing, we can eliminate pain, restore the airway, decrease discharge and toxemia, protect the lungs from chronic changes, and eliminate a focus of infection. If we should also obtain relief from asthma, then we would be doubly rewarded."

Cummings⁷⁸ stresses the value of bronchoscopy, with instillation of ephedrine through the scope; this may relieve status asthmaticus.

Penicillin is now widely used in infectious processes in the nose and sinuses; inhalation therapy has recently been added to parenteral, and a few use oral treatment.

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Schenck³⁰⁰ notes a definite reduction in sinus surgery since the introduction of antibiotics for acute and chronic sinus infection. When allergy is also present, these antibiotics are of lesser aid. Chronic infection of sinuses with extensive irreversible tissue changes of allergic origin, says Schenck, can rarely be influenced by chemotherapy alone and eventually demands surgery. Rendi²⁸² recommends treatment with penicillin for all acute and chronic inflammation of the accessory sinuses due to infection; those due to allergy are not too favorably affected. Intramuscular and local penicillin therapy gave excellent results in five cases of chronic pansinusitis with polyposis.

Barach and his associates²⁴ used penicillin aerosol and negative pressure in the treatment of sinusitis. There was good improvement in forty-seven cases of acute and chronic sinusitis, some complicated by asthma and nasal allergy. But allergic patients showed less improvement than infectious. Sulman³³⁰ treated sixty-one patients with various upper respiratory infections with Par-Pen (Paredrine hydrobromide 1 per cent and 800 units of penicillin per c.c.). The medication was used locally in the nose and sinuses. Excellent results were obtained in fourteen patients, good in forty-one, and fair in five. No toxic reactions were observed.

Lymphoid tissue in the nasopharynx has been removed by radium or radon in an increasing number of cases. In reviewing the histories of children being treated for deafness, Crowe and Walzl⁷⁶ observed that some who also had asthma showed concomitant improvement in their asthmatic condition during radium treatment. Several hundred such children have been treated and carefully studied by an otolaryngologist, an allergist (L. N. Gay), and a pediatrician. Encouraging results have been obtained in cases due to "bacterial" allergy, but, as would be expected, the atopic conditions receive less benefit. But in both groups, irradiation of the nasopharynx removes lymphoid tissue and thereby lessens mechanical obstruction to breathing and hearing as well as chronic infection. These findings are confirmed by Crowe⁷⁷ and Gay.¹³⁸ Gay points out that recurrence of adenoid tissue was found in 795 of 1,365 school children whose tonsils and adenoids had been removed. Removal of this adenoid tissue, says Gay, has led to dramatic relief from perennial rhinitis and asthma in many cases. It is wise to complete the treatment during the summer when infections are less prevalent, and no exposures should be made during acute infections. Dosage: the first is so small that, with proper application, complications cannot occur. The second exposure is usually given four weeks later, the third four weeks later. Examination of the nasopharynx determines the need for any and all exposures.

Ward and his co-workers³⁶⁷ treated thirty-four asthmatic children who had lymphoid hyperplasia in the nasopharynx. Radon exposures (2 gm. minutes to each side monthly for an average of four treatments) caused complete disappearance of the lymphoid tissue in twenty-three of these thirty-four children, and fifteen children were completely relieved of their asthma; five others had mild attacks only, and three were improved. The type of asthma has no apparent bearing on the success of treatment. Proctor²⁶⁹ treated 400 patients with radon exposures; of these, nineteen had asthma, nine ceased to have attacks, and five others were markedly benefited.

Grove¹⁵⁰ continues to urge surgery for sinusitis. He admits that in the primary state of the hyperplastic type of sinusitis, allergy is present in almost 100 per cent of the cases and that eosinophils are often present in the nasal smears. Yet he insists on "adequate" sinus surgery: to get good results, the entire diseased mucous membrane must be removed; in those asthmatic-sinusitis patients in whom this was done 79.8 per cent were improved; if only partial removal was carried out, only 35.2 per cent were successful. His statistics are based on 200 asthmatic patients operated upon. His best results from surgery were in those whose asthma began after twenty-one and in whom the duration of asthma was less than ten years. He advises usual allergy measures postoperatively.

Thacker³⁴¹ is less radical. He uses nasal sprays, Benadryl, aminophylline for associated asthma, avoidance of allergens and desensitization with specific allergens, conservative nasal surgery when indicated, injections of histamine, and injections of the turbinates with a sclerosing agent if all other measures fail. Bernardino²⁹ applies Bovain solution (phenolized cocaine) to the nose of patients with asthma in whom previous therapy failed. Improvement results, with unknown mechanism.

BACTERIAL ASTHMA

Frouchtman¹²⁸ surveyed the air in Barcelona, Spain. Besides molds, he found that sarcinae and diphtheroids predominated. Bacterial counts increased in spring and decreased during the summer. He obtained good results in twenty-six asthmatics

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by injecting vaccines made from these bacteria, with complete relief of asthma in twenty-two cases for periods of several months to more than a year. The aerobacteria, he states, are capable of specific action, either in stimulating the appearance or conditioning the chronicity of respiratory allergic diseases. Blamoutier and Guilbert³⁴ obtain good results in the treatment of bronchitis, with or without associated asthma; they use a polyvalent vaccine. Brauer⁴⁴ shocks the asthmatic patient by intravenous "pyrifer" therapy with *B. coli*; only failures from previous treatments are used, and the author has carried out this measure for over ten years in a fairly large series of cases and with no unduly severe reaction. The injections are always given in the free intervals between, not during, attacks.

Scherp's paper³⁰¹ deals with hypersensitivity to infectious agents in relation to asthma. He points out that bacteria, molds, viruses, et cetera, can cause symptoms by (1) a non-immunologic process (direct action of organisms) and (2) an immunologic, which may act either by anaphylaxis, as with allergy, or by a tuberculin-like reaction of the delayed inflammatory type which may go on to necrosis. Skin tests in the anaphylactic type give prompt whealing and erythema; in the tuberculin type the tests are delayed and inflamed, and may be associated with infection in any part of the body, e.g., the cornea, kidneys or meninges. He states that extrinsic asthma can result from fungi, but does allergic asthma occur on a significant scale when the source of the provocative antigen is a focus of infection within the body?

Weil³⁶⁹ brings up the point that one group of workers says that bacteria may be factors in the strictly allergic diseases, e.g., bronchial asthma. A second group says no, and the rest say nothing. As in the successful proving that pollen in the meadow causes hay fever, so must we investigate pathogenic and nonpathogenic micro-organisms, including viruses, in a whole-hearted effort, by every possible method. Then, and only then, says Weil, will we be able to "state with any degree of confidence whether or not microbial antigens are involved in a given manifestation of allergy. Maybe a few years hence we shall be able to talk less about conjectures and more about facts."

Fondé¹¹⁸ writes about hypersensitization in chronic infectious diseases, and says that the method of diagnosis and treatment which he outlines for brucellosis and malaria might well be applied to other persistent infections. Agustí Coranti⁷ has obtained good results in seventy-nine cases of asthmatic bronchitis (in Barcelona) by injections of an Anti-Alpha vaccine; there is a tuberculous factor, he says, in 90 per cent of asthmatic bronchitis.

ASTHMA IN CHILDREN

Asthma in children has been mentioned all through this review. In addition, there are a few articles specifically limited to this subject. Bowen's paper¹⁰ on management of asthmatic children is excellent. It is very practical and informative, and covers all angles of treatment, including history-taking, examination, nasal problems, chest complications, food and inhalant allergens, methods of testing, drugs used for treatment, immunologic measures, and last, but not least, the psychological aspects of the asthmatic child.

Another excellent article is the annual critical review of pediatric allergy by Glaser.¹³⁹ It has a fine section on asthma in children, especially as regards differential diagnosis. Benadryl is disappointing in bronchial asthma, although an occasional child gets definite relief, especially in food-sensitive cases; Benadryl is useless in intrinsic asthma. In another article on symptomatic treatment of bronchial asthma in infancy and childhood, Glaser¹⁴⁰ gives practical suggestions, such as use of drugs, nose drops, and house cleanliness.

Ratner²⁷⁷ uses aminophylline, small doses of epinephrine, and, above all, he gives syrup of ipecac, a teaspoonful each hour till emesis occurs. [A very valuable procedure which often leads to quick relief.] He stresses the necessity for a cheerful attitude, and advises 300 to 500 c.c. slow drip 10 per cent glucose intravenously. For sedation, he uses rectal retentions: 10 to 15 grains bromides, $\frac{1}{2}$ grain phenobarbital, 2 to 7 grains chloral, or 1 to 2 teaspoonful of ether in 1 to 2 ounces of oil. He dislikes epinephrine in oil, though most workers use this at all ages, and he never uses morphine. Chobot⁶⁶ gives much the same treatment, though he uses codeine gr. $\frac{1}{2}$ to 1 in a suppository, and also recommends 50 to 100 mg. Demerol.

Holt¹⁷⁰ states that mild attacks of asthma can sometimes be aborted by teaspoonful dosages (eight-year-old child) of Elixir of Neo-Synephrine, with or without a mild sedative; injections of epinephrine still remain the best treatment for severe asthma. Lapage²⁰⁶ emphasizes the necessity for raising the hygienic level of the child. For attacks, he advises adrenaline, potassium iodide, belladonna, lobelia,

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stramonium, ephedrine, aminophylline, and, in exceptional cases only, morphine. Pedrera in Havana²⁶⁰ found excessive nervous reactions on the part of the mothers when he injected adrenalin in oil in children. So he now uses the 1:1,000 solution in doses of 2 to 3 minims as necessary.

TREATMENT OF RELATED CHEST DISEASES

Meade and his associates²³⁴ performed 196 lobectomies at the Kennedy General Hospital Chest Surgical Center from 1943 to 1946, with one death. The patients were twenty to fifty years old, the majority under thirty. Indications for lobectomy were: bronchiectasis in 161, cyst in twenty-two, chronic suppuration in nine, bronchial adenoma in two, actinomycosis in two. Penicillin was given by all routes before, during, and after most of the operations. One patient died twenty hours after lobectomy for bronchiectasis; empyema occurred in fifteen, jaundice in seven, pneumothorax in two, and hemothorax, atelectasis, and cerebral embolism in one each. [These results, in so difficult a procedure, are simply outstanding, and should make us all the more eager to refer our bronchiectatic patients as quickly as possible for lobectomy; there is no other effective treatment for this condition.] In another paper, Kay, Meade and Hughes¹⁹⁴ report 258 consecutive lobectomies with only one operative death, an incidence of 0.4 per cent. This number included the 196 noted above.

Bisgard and Swenson³² report four cases of bilateral bronchiectasis cured by bilateral lobectomy. In all cases, the two lower lobes and in one case the right middle lobe were removed. Three of the four patients are symptom-free; the fourth has some residual cough and sputum because bronchiectasis is still present in the right middle lobe and in the lingua of the left upper lobe. Each side was operated separately.

From the Lahey Clinic, Adams and Ficarra analyze fifty consecutive, surgically treated cases of bronchiectasis in the five-year period ending August 31, 1945. The end results: no hospital deaths and no deaths recorded during the follow-up period. Forty-two patients are apparently cured. Early surgery is rightly advised, as lobectomy gives excellent results.

Harper²¹⁶ instilled Iodochloral (Searle) (22 per cent iodine and 7.5 per cent chlorine in organic combination with highly refined oil) in forty-three cases of bronchiectasis, ages seven to sixty-five. Results were good in twenty-eight patients (65.8 per cent), fair in eleven (26.3 per cent), poor in four (7.9 per cent). One instillation of the oil was used in thirty-two cases, but a second was done in eleven because the patients requested it. Kooperstein and Bass,²⁰² however, report three cases of bilateral pneumonia which followed intrabronchial instillation of iodized oil. The pneumonia did not develop for more than a week. The patients all had bronchial asthma. Mahon²²⁷ notes that fatalities are rare after iodized oil is instilled, though reactions, e.g., swelling of the parotid and submaxillary glands, asthma, urticaria and dermatitis, are not uncommon. His patient, forty-one, male, died about one hour after instillation into the bronchi. The patient had a history of slight cough but no asthma, yet, on postmortem, the bronchi and bronchioles were filled with thick inspissated mucus and there was a generalized eosinophilia, all suggestive of asthma as a cause of death. [All patients should be given 1 to 2 minims of potassium iodide before iodized oil is instilled.]

MISCELLANEOUS INFORMATION REGARDING ASTHMA

The following are listed under the heading of "Misbranded Products:" Asthma Tea, Manning's Asthma Plaster and Salve, and Himrod's Asthma Powder.¹⁷⁸

The National Home for Jewish Children continues to do a fine job for asthmatic children. More such institutions should be started. Its program for the care and rehabilitation of asthmatic children is ably set forth,¹⁶ and Peshkin, the chief consulting physician, deserves much praise. The home is most attractive, and the children do well. A recently made "movie" of the home is available.

The Brandes School in Tucson⁵ is also doing good work. In the seven years of its existence it has had 300 students; sixty-seven were enrolled at the end of this past year; thirty-seven of these came because of asthma, and four of these also had hay fever; in addition, six had hay fever alone, sixteen perennial rhinitis, six sinusitis, and eleven frequent upper respiratory infections perhaps associated with allergy. Most of the children live normal lives, chiefly outdoors. In the thirty-seven asthmatic children there was only one incident where a physician had to visit a child. Some had occasional mild asthma, requiring an occasional tablet of ephedrine or the epinephrine spray. On visiting parents during vacations, three developed severe

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asthma—psychic? Most children continued to improve when they returned to their homes. Neidoff confirms these good reports.

The study of asthma and allergy is spreading all over the world.²⁵⁰ In Krakow, Poland, a new society was formed to prevent and fight asthma. There are 220 members, most of whom are asthmatic patients. The French Society of Allergy met in June, 1947, with reports on house dust and antihistaminic drugs. The first scientific meeting of the Italian Association for the Study of Allergy was recently held in Milan. The papers which were read will soon be published in the *Quaderni della allergia*.

Well-organized allergy clinics, reports Wittich, returned from a tour, are in operation in Colombia, Peru, Chile, Argentina, Uruguay, Brazil, and Havana. Mexico has made great strides, and there is a Mexican allergy society, which is doing good work in teaching and aiding in the care of patients.

Francis¹²¹ has a long article regarding a report of a committee on Workmen's compensation of the Society for the Study of Asthma and Allied Conditions.

Forman¹¹⁹ discusses the treatment of elderly asthmatic patients. Besides the usual therapy he likes 100 mg. doses of Syntropan. He often gives the following prescription:

Potassium iodide	8.
Caffeine citrate	1.60
Ephedrin Hydrochloride	0.60
Syr. aurantii	20.
Aquae q.s. ad	120.

Sig. Teaspoonful in water on awakening
and at 10 a.m., 2 p.m. and 8 p.m.

The prognosis in asthma is discussed by Aarsvold.¹ In a follow-up of 147 asthmatics who had not been subjected to specific desensitization, after a period of five years, 23 per cent were free from symptoms and 63 per cent improved. Another group received specific desensitization, yet the results were about the same. Surinyach Oller³⁸³ also writes on prognosis; this depends on the correct diagnosis.

And, finally, the usual number of general papers on asthma has appeared, many very good, with excellent reviews of the subject. Among the authors are Laird,²⁰⁵ Aschner,¹⁸ Harris,¹⁵⁷ Serra-Godoy,³¹² Wolfer-Bianchi,³⁷⁶ Epstein,¹⁹⁶ Gauguly,¹³⁵ Carr and his associates,³⁷ Waner³⁶⁶ Squier,³²⁵ Schroeder,³³⁷ and Detweiler.⁹⁰

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PEDIATRIC ALLERGY

A Critical Review of Recent Literature

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PSYCHOSOMATIC CONSIDERATIONS

The literature on the subject of psychosomatic medicine in the process of its steady growth has fortunately not neglected the subject of pediatric allergy. To do justice to this literature, the reviewer should be a combination of pediatrician, allergist and psychiatrist. Unfortunately, in this instance, the reviewer is not a psychiatrist, and the subject is therefore presented as seen by the pediatric allergist. It is well known that emotional disturbances, fatigue and other similar factors can of themselves precipitate an asthmatic attack. Mirvish⁶⁷ stresses the fact that failure to handle this aspect of the problem can wreck the most carefully devised scheme of medical treatment. The child as well as the disease must be treated. This demands a knowledge of the patient's entire psychological background—his relation to his parents, relatives, friends, and teachers. The family practitioner is in the best position for this study of the child, and the knowledge so gained is of the utmost value in treatment.

Mirvish gives an outline for a questionnaire with respect to the parents and the school child. He also gives some general instructions. The first of these is for the parents to be patient. There is no quick road to recovery and ups and downs are to be expected. The parents are warned that the child is easily affected by the attitude of people about him. A happy, cheerful atmosphere tends to keep the condition in check, whereas an atmosphere of anxiety, nervousness, or tension is liable to precipitate an attack at any age.

As far as possible, the use of the term "asthma" or "attack" either in the presence of the child or others is to be avoided. The child's ailments should not be discussed with other people, particularly in his presence, nor should he be compared with other children in his own presence. The child should be encouraged to sleep alone. During an actual attack, excitement and panic are to be avoided. If the child is wheezing very mildly, do not draw his attention to it as this emphasis is almost certainly apt to make the attack worse. Fatigue must be guarded against. The commonest causes of chronic fatigue in the school child are: (a) insufficient rest, (b) irregular feeding habits, (c) too many "extras" as music, dancing, et cetera. The child must be treated, as far as possible, not as an invalid but as a normal child.

Fisher³¹ also agrees that too much attention is paid to the detailed study of the child and not enough attention is paid to the study of the child in his normal surroundings. He feels that it is important to avoid what he calls the establishment of the "asthma habit." The child victim of allergic disease has inherited an ill-balanced autonomic nervous system; there is an abnormal sensitivity of certain local cells—in asthma, those of the respiratory tract—and this probably persists in active or latent form throughout life.

It is a matter of clinical observation that in the early years of life, emotional excitement, especially if accompanied by some degree of physical exhaustion, is one of the two main exciting causes of the asthma attack. The other, climatic variation, is largely beyond our control. Underlying specific sensitivities may be present and we must ever be on the watch for them, but the excessive emotional reaction is the most commonly blamed denominator. As the child grows older, his emotional instability becomes gradually more and more under the control of the will. The parents must avoid undue emphasis on the child's condition and must assume an air of quiet, placid confidence that the chest trouble is a childhood complaint which is not going to persist. Attacks may be expected to occur when the child enters school, induced by the novelty and excitement of this procedure. The child should be helped through this period with the appropriate medications so that he does not develop a fear of attending school. Undue emphasis should not be placed on the fact that certain foods, circumstances or environments are likely to bring on an attack. Adequate hours of rest and sleep must be insisted upon, and loss of sleep due to asthma must receive full compensation during the

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day. Drastic dieting is to be avoided. Operative procedures in the upper respiratory passages should seldom be undertaken except for the elimination of infection or relief of obstruction secondary to chronic infection.

According to Swanton,¹⁰⁵ the personality of the preasthmatic child is nervous, excitable, irritable, aggressive, and dominating. He states that he has never seen an asthmatic child with a low intelligence quotient. (The reviewer has seen several.) The personality of the parent of the asthmatic child is overanxious and overprotective. The personalities are so much alike that it is inevitable that they will clash. The child is therefore frustrated by the parent, and this frustration creates an emotional reaction which his environment forces him to control. Swanton suggests that it is this inhibition of his natural emotional responses that is reflected in abnormal reactions of the patient's autonomic nervous system, and expressed dramatically as asthmatic attacks.

It is an interesting fact that there are more childhood than adult asthmatic patients. Swanton offers as a psychological explanation that the child becomes more mature and independent in his teens and tends to grow away from his parents and their rigid control. He is therefore less subject to parental frustration. He directs attention to the similarity between stammering and asthma. Stammering has many similar characteristics to asthma in that it appears to be an inco-ordination of the glottis associated with expiratory efforts which are due to psychological factors producing inhibition in those children who suffer from the stammering diathesis. For instance, the stammerer demands an auditor or he does not stammer. A child stammerer may talk to himself alone, read aloud alone, sing, and so on without a trace of a stammer. One characteristic of the asthmatic is his suggestibility. It has long been recognized that suggestion can precipitate attacks and conversely that suggestion can be a potent force in relieving attacks. In the case of children, psychological treatment is almost solely a case of parent education, and the treatment should fall within the sphere of the family physician. As in most of the nervous disorders of childhood, it is rarely necessary to see the child. In fact, Swanton states that it is quite dramatic to see a child with asthma "cured" by one or two sessions with a co-operative parent. The reviewer, who has never seen this happen, agrees that such instances would be highly dramatic. However, one would like to be sure that these children actually suffered from bronchial asthma and not from a condition such as sighing dyspnea, for example. If Swanton sees the child, he does no more than tell him quite confidently how glad he is that the child is growing up and getting stronger and that he is quite sure the child's troubles are over and that the attacks of asthma will soon cease. He tends to convey to the child the impression that the attacks are quite unimportant and that as a physician he is completely unconcerned about them.

Gerard⁸⁸ makes the interesting observation that evidence does not support the assumption that allergic sensitivity in conjunction with strong emotional states equals asthma. Since allergists have found no substances which are specific only for asthma and not for other allergic conditions, recent investigators have turned their attention to an analysis of the personality structure of asthmatics in an attempt to unearth the psychic complex, if any, from which the emotional states observed in asthmatics may arise, and which are conflicts common to all asthmatic patients. This is the approach which has proved of most value in the explanation of the production of other psychosomatic disorders, such as ulcer, constipation, enuresis and others. The author quotes extensively the work of French, Alexander, et al⁸² in which she participated. This was a meticulous study of sixteen adults and eleven children. Five more children were added in the present study. It was concluded that the asthmatic attack occurred as a reaction to the danger of separation from the mother or loss of her love.

Situations which stimulated the fear of loss of the mother were found to be of two kinds: one, the prospect of actual separation from the mother; and two, a temptation situation in which repressed impulses of which the mother disapproved threatened to break through and estrange her. The impulses most commonly considered dangerous to the patient were sexual impulses. The patients disclosed a variety of defenses against fear. Most common were those seeking reconciliation, such as the utilization of suffering to gain sympathy, and confession of wishes which sought maternal acceptance of the wishes.

Attacks were found to occur when the defenses broke down. Two main situations causing disintegration of the defenses occurred when the danger of losing the mother became acute and when the threat of estrangement took the patient by surprise. The character structures of the patients varied considerably, but common to all were a lack of independence and immaturity as well as a dependent attitude toward the mother and maternal figures. During analysis, interruption of

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the asthmatic attack occurred in several situations. In some, confession relieved the attack. In others, crying caused the cessation of attacks, and this indicated to the authors that there was a correlation between the asthma attack and the inhibition or repression of a cry which arose from anxiety or fear.

The author very fairly does not ignore a constitutional factor. Since it was proved that under certain circumstances the asthmatic attack did not occur when the patient was thrust into specific complex situations in the absence of allergens, it was suggested that the basic emotional conflict operated to make the patients less resistant to the allergens. These findings seem to offer strong evidence that the specific emotional condition of the patient is at least of equal importance to the allergic sensitivity in the production of asthmatic attacks.

Saul⁹² makes the point that whereas in peptic ulcer the patient's story is usually one of frustration resulting in overwork, excessive demands, and lack of ease, support and health, in hypertension the story is usually that of drive, competition, aggression, and hostility; in patients with allergic symptoms the material is usually strikingly different. Here the story is commonly that of libidinal frustration. The various methods of close attachment of the mother to the child—oral, dermal and respiratory—are discussed, and allergic reactions in these tissues are seen as expressions of the individual's attempts to return to the early relationship between mother and child. The few case reports which the author uses as illustrations are interesting and suggest that these ideas merit serious consideration. The cases are, however, not reported in sufficient detail, to be convincing to the allergist who is accustomed to studying these patients by orthodox techniques.

The psychologic aspects of allergic skin disorders have been made the subject of a splendid study by Woodhead.¹¹⁵ She studied twenty-six cases of allergic skin disorders referred from the Dermatological Department of Guy's Hospital, including infantile eczema, Besnier's prurigo (which in this country we now most commonly term chronic atopic dermatitis), and two cases of papular urticaria, all of which had failed to respond to the usual methods of treatment.

Of twenty-six children investigated, four were the eldest in the family, ten were the youngest, eleven were only children, and only one occupied a position in the middle of the family, and this last child was in an isolated position in that her brother was five years older and her sister seven years younger. These children all occupied a special position in the family which rendered them more susceptible to any psychological difficulty of their parents. With one exception, all the children in this series had an intelligence well above the average. They were determined and aggressive even to the point of narcissism. They were also sensitive and had many fears and were thus insecure. These children reacted to life's problems with attacks of eczema. In most instances these problems resulted in psychologic maladjustment to the parents, from which the child must be freed so that he can develop his own personality and then deal with life by normal methods and not by an allergic attack which acts as a defense against life.

In contrast to Swanton, Woodhead recommends psychological treatment of the child and states that in some instances it is given to the parents as well. When the child improves, the parents may improve also; in other cases the parents' problems may get worse as they seem to project their problems onto the child.

A different point of view is expressed by Henderson⁵¹ who quotes Sir John Freeman to the effect that an allergic reaction to a protein is but one of the links in a causal chain which may contain other links, including nervous factors. Henderson criticizes those investigators who report success in the treatment of asthma by means of psychosomatic technique in cases where the allergic approach is not thoroughly studied and quotes several illustrative cases which might have been explained on a psychic basis but which were satisfactorily managed from the standpoint of allergy. Henderson has the impression that most of the cases of bronchial asthma investigated by psychiatrists are psychoneurotics with bronchial asthma. Only in rare instances would the disease appear to be originally psychogenic and even then careful search will usually reveal that a state of allergic equilibrium has been upset by the psychic trauma. There probably are some patients who consciously or unconsciously utilize their disease to excuse their deficiencies, and even to achieve their ends. In the case of children the attitude of the mother is of real importance. Much wisdom and restraint are called for. Overprotection and apprehension are most unwise and may serve as a "trigger mechanism" through suggestion. The child should not be taught that he is an invalid and therefore be wrapped up in cotton wool. A little healthy neglect may even be preferable to oversolicitude.

Deutsch and Nadell²¹ attempt to illustrate the psychosomatic factors which are the presumptions for the development of chronic allergic and related skin conditions. These they formulate as (1) skin conditions in earliest infancy, probably

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originating on a genetic basis; (2) deviation or fixation of instinctual drives during the earliest psychic development, and fusion of these with the different sense perceptions related to the skin; (3) complimentary neurotic traits of the environment favoring the amalgamation of the psychosomatic entity, and (4) development of a narcissistic and exhibitionist personality pattern tinged with compulsive neurotic traits.

In concluding this section, the reviewer cannot refrain from expressing his own opinion regarding the psychosomatic approach to the problems of allergy, because, as stated above, any help which the psychosomaticist can give in this field will be most gratefully received by the pediatric allergist. First of all, the problem would be helped considerably if the psychosomaticist, in writing his papers, would state, if he believes it to be true, that some but not necessarily all cases of allergic disease are on a psychosomatic basis. With this the pediatric allergist certainly could not quarrel and would not be prejudiced by the expressed or implied assumption that all cases of allergy are due to disturbances of the psyche. Secondly, it would be of great service if, in writing his papers, the psychosomaticist would bear in mind that he is writing for pediatricians and allergists as well as other psychosomaticists and would simplify his language so that it can be more easily understood by the pediatric allergist. This, of course, is an old criticism of psychologists and psychiatrists which many appear to have seriously considered.

The application of a psychological approach to problems of allergy in pediatrics is exceedingly difficult, and such studies as have been abstracted above are greatly to be commended. However, the general principle that a chain is no stronger than its weakest link holds true here. Under stress and strain of psychic origin the weakest link will give way, and in the case of an allergic child an allergic response may logically be expected. The child with an allergic manifestation will soon discover that he can use this as a defense in a difficult situation the same as any other child with any other illness can use that particular illness. In proportion as a child's allergies have failed to respond to the efforts of his physician, so will a child feel less and less secure—a situation which is worsened by the increasing anxiety of the parents as this state of affairs becomes increasingly manifest. That abnormal psychological situations should occur under such circumstances is only natural. At this point it may also be pointed out that most of the studies of psychomatics with respect to allergy have been done on chronic cases in whom, as stated above, a chronic abnormal psychological situation may reasonably be expected to have developed for reasons mentioned above. However, the best that can be hoped from the psychological approach is amelioration;—rarely a cure, because no psychological approach can change the underlying allergic constitution. Every allergist has had the experience of seeing some new therapeutic advance relieve an occasional patient, and under these circumstances the associated psychosomatic problems vanish like mist in the sun. In this connection one need only mention instance of urticaria of years' duration which have received adequate symptomatic relief from Benadryl or Pyribenzamine, resulting in an entirely new outlook of life on the part of those patients. Once we are able to relieve at will the allergic manifestations, the psychological problems associated will, in most instances, solve themselves, although in a basically psychopathic individual the clinical manifestation of the abnormal psychologic state will of course express itself in some other form.

ATOPIC DERMATITIS

The statement of Cook¹⁴ with regard to the uselessness of scratch and intradermal testing in atopic dermatitis (infantile eczema) has been discussed in a previous review.^{43c} Cooke's statement has been more recently considered by Hill,⁵² with whom the reviewer is in complete agreement. Hill cannot agree that the urticarial type of reaction gives no information; the allergen which produces the reaction gives either urticaria or eczema depending upon the circumstances. Hill gives a number of cases illustrating eczema produced by such substances as egg and milk which gave positive scratch tests. The process taking place in the capillary vessels in atopic dermatitis may be looked upon as subclinical whealing (Sulzberger). It is possible according to Hill, and the reviewer is in complete agreement with this, that too sharp a distinction has been made between atopic and contact dermatitis. It seems clear that patch tests may occasionally give valid information in infantile eczema.

Hill states there is some reason to believe that once a baby is sensitized in a high degree to egg, fish or other foods, this fundamental underlying severe primary sensitization renders him more likely to acquire lesser secondary sensitizations to food which he eats every day. The normal infant for a short time after

the ingestion of a new food may show positive intracutaneous tests to that food. Scratch tests are not positive, and the positive intracutaneous tests may last for weeks or months rather than for years. While it is known that milk protein may pass through the intestinal barrier with great regularity in early infancy, it does not do so commonly in later childhood (Schloss), and probably even more rarely in adult life. However, the young infant fed on cow's milk is taking an enormous quantity of protein in relation to his weight, about 40 grams daily if he takes a quart of cow's milk. He was not intended by nature to take such a large amount; in a quart of human milk there is only about 15 grams of protein. According to Hill, the infant must have absorbed unsplit food protein at some time in order to have developed a positive skin test. However, it is well known that young animals of any kind form antibodies very poorly and it takes them a long time to do so. If, after a short time, the infant no longer absorbs unaltered protein, which is often the case, the positive scratch test is without etiologic significance.

In a later publication, Hill⁵³ again makes the statement that he is convinced that sometimes an allergen which gives a positive urticarial-type skin test may also cause atopic dermatitis. Of thirteen infants with positive skin tests to milk, all of which were of etiologic significance, and who were either greatly improved or cured by feeding soybean milk, seven developed positive skin tests to soybean at varying intervals of two to four weeks.

As far as hyposensitization to any environmental allergen in atopic dermatitis is concerned, Hill⁵³ states that it does not seem logical that when the allergen has been reaching the skin by inhalation to do this unless the patient has been removed from his environment, and the procedure can be compared to the preseasonal treatment of pollinosis. The reviewer feels, however, that there is a certain logic to the treatment of atopic dermatitis in some instances with an environmental allergen, even though the infant cannot be put into an environment completely free from that allergen. This may be compared to the co-seasonal treatment of pollinosis which is, occasionally, very helpful.

Hill's observations also suggest that although respiratory allergy and atopic dermatitis are both accompanied by positive wheal reactions which are apparently identical, the immunologic situation in the skin may be, in reality, different in the two disorders and that some added factor is necessary to insure the production of dermatitis. He here states that if one could discover this factor one would then be able to tell why a particular organ is selected as a shock tissue by a particular allergen. This knowledge would be of fundamental value.

Simon⁹⁹ has continued his interesting studies in the relationship of human dander and other inhalants to atopic dermatitis. He notes that the incidence of cutaneous reactions of the characteristic atopic type with patch tests to human dander are very much greater in patients with atopic dermatitis than is the incidence of such reactions (1) in general population or (2) in patients with hay fever and asthma but without atopic dermatitis. The same is true of the incidence of cutaneous reactions of the urticarial type to scratch or intracutaneous tests with human dander, and the incidence of these reagins for human dander in the blood. Although two years ago it was Simon's opinion that surface contact of the skin with human dander might be an important factor in the production of atopic dermatitis, he now feels that the mere contact of the skin with human dander is not an important etiological factor. Unpublished studies by the reviewer confirm this opinion.

Attempts to detect the presence of dander allergen in normal skin scales from the general body surface have been unsuccessful. A reactive substance has been found in the scales of certain cases of seborrheic dermatitis, and reagins for this substance have been found in patients with atopic dermatitis. These reactions do not parallel those to human dander. The reviewer feels that these latter observations of Simon are of extreme importance. The pediatrician very often observes cases of what appear to be typical seborrheic dermatitis pass almost imperceptibly into typical atopic dermatitis. Simon's observations appear to be the first scientific evidence of a relationship between these two cutaneous disorders.

Trudeau¹⁰⁷ notes that there are two principal varieties of infantile eczema: one of internal origin, which he terms essential, and another of external origin, which he terms accidental. He emphasizes the nervous elements in this disorder. In discussing treatment, he mentions the use of autogenous vaccine. The reviewer would consider this to be a form of nonspecific therapy. The discussion is general and without case reports.

The subject of the hospital morbidity and mortality of infants with eczema and also hospital boarders has been reviewed previously.^{43a} Among the papers reviewed was that of Schwartzman⁹⁶ who has continued his studies.⁹⁷ These were carried out on seventy-one cases of eczema and 230 boarders for the period

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January 1, 1942, to January 1, 1946. In a comparison with figures of similar studies for the period 1934 to 1942, it was demonstrated that the morbidity and mortality rates were higher in the present study. This is interesting in that Schwartzman feels that the general use of sulfonamides and antibiotics has caused no material change in the results, and he therefore feels that despite the great proven value of these therapeutic agents, complacency cannot be tolerated as regards boarders and eczemas. This is in disagreement with the work of Epstein²⁵ previously reported.^{43b}

In Schwartzman's⁹⁷ present study there were thirty-eight cases of eczema admitted without complications. Of these, 65.8 per cent contracted cross infections and 2.6 per cent died. This one death was in the case of an infant under two years of age. Of the thirty-three eczema patients admitted with complications, 45.4 per cent contracted additional infections and 6 per cent (two patients) died. Both of these were infants under two years of age. The morbidity for the fifty-two infants with eczema was 56.3 per cent and the mortality 4.2 per cent. This is a definite increase over the morbidity and mortality of the years 1934-1942, a morbidity of 48.8 per cent and a mortality of 2.3 per cent.

In the 1942 to 1946 series of boarders, there were 230 cases with a morbidity of 35.2 per cent, as contrasted with 128 cases in previous years with a morbidity of 5.5 per cent. There was no mortality among the boarders at any time. The increase of morbidity to an extent almost seven times as great as the 1934 to 1942 group among the boarders is difficult to explain, because all boarders had been segregated on a special ward during the latter series, whereas formerly there had been none provided for them. The explanation which the author offers as a possibility is the great scarcity of experienced help during the war period.

VACCINIA COMPLICATING ECZEMA

A case of generalized vaccinia complicating eczema is reported by Stiller.¹⁰⁰ This was a one-year-old girl who had had eczema since the age of five months. This appeared to have become infected two days prior to admission to the hospital. The lesions had the appearance of generalized vaccinia, and the history revealed that a sibling had been vaccinated several days before the onset of the infection. The child was treated by the injection of penicillin, and the temperature returned to normal within twenty-four hours and the child was discharged after five days. The author points out that at times the skin lesions of generalized vaccinia may be severe enough to resemble confluent smallpox and that one-third of these children may die. However, the reviewer believes that this mortality has been considerably reduced since the advent of the sulfonamides and the antibiotics. This case illustrates the fact, emphasized by the author, that vaccination should not be done in families where there are unvaccinated members suffering from eczema.

TREATMENT OF ATOPIC DERMATITIS

A comprehensive review of their work on the relationship between eczema and essential fatty acids has been published by Hansen and associates.⁴⁸ They state, very fairly, that it is yet to be demonstrated that the fatty acids known to be essential for experimental animals are required in human nutrition. For supplying unsaturated fatty acids, fresh lard in quantities of 1 to 2 ounces a day was used for the largest series of patients. The largest amount of lard given was 1 ounce three times a day. Raw linseed oil and corn oil were also used. Usually, clinical evaluation could be made within one to two months after introducing this therapy, but sometimes the therapeutic effort was continued for a longer time. The authors state that of 148 patients receiving some form of unsaturated fatty acid therapy, there were sixty in whom the results were good to excellent, fifty-one in whom the results were fair to good, and thirty-seven in whom response was either poor or lacking. The most unsatisfactory results were in the older groups. These results correspond with the finding of the iodine number of the fatty acids of the blood serum below the normal range in 82 per cent of the infants under two years of age, 74 per cent of the patients between two and fifteen years of age, and 55 per cent of the adults. A very interesting point brought out by the authors is that there is an increase in the unsaturated fatty acids in patients treated by tar. This finding may lend some support to the theory that tar preparations affect the lipid metabolism of the tissues. It is also interesting that cow's milk is relatively low in essential fatty acids, while there are appreciable amounts of linoleic and arachidonic acid present in human milk. This is significant in relation to the observation of Grulee and Sandford⁴⁵ that eczema occurs seven times as frequently in artificially fed infants as in those maintained on breast milk.

With respect to the influence of infection, a point of clinical interest is the fact

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that eczematous eruptions are almost invariably made worse when infections of the upper respiratory tract are present. This does not correspond with the reviewer's experience that infections of any kind, if accompanied by fever, nearly always have a beneficial effect upon the eczematous process.

The authors state that the over-all experiences of themselves and others would appear to indicate that the inclusion in the diet of fats rich in unsaturated fatty acids is of definite benefit to the majority of eczematous patients even without other forms of therapy. The authors emphasize the fact, which the reviewer notes is often overlooked, particularly by firms promoting the use of preparations said to contain unsaturated fatty acids, that the addition of unsaturated fatty acids is not a substitute for other therapeutic measures in the control of infantile eczema.

Stoesser¹⁰² has reported on seventeen infants ranging in age from three to fourteen months. Eleven had severe eczema with oozing and crusting; the remainder suffered less severely. Sensitivity to cow milk was determined by trial diet or by the cutaneous test. Instead of cow milk, the infants were fed a soybean food (Mullsoy) to which had been added 4 per cent soybean oil with an iodine absorption value ranging from 119 to 135. The infants with the more severe skin damage had iodine numbers averaging 71, which is much below normal. After three or four weeks on the above preparation, the values rose until 118 was reached. This situation was associated with a favorable response to external therapy. In the other group there was little change in the iodine number and the total serum fatty acids. Stoesser feels that there is some correlation between the level of the unsaturated fatty acid of the plasma lipids and the type and course of infantile eczema. He also states that observations in this study confirm previous findings in which it is noted that during an acute infection of the upper respiratory tract in infants with eczema, the skin showed temporary improvement at the onset of the fever but was much worse thereafter. He associates this with previous observation to the effect that in an acute infection there is a sudden flow of unsaturated fatty acids into the blood stream, followed by a fall to abnormally low levels.

Hapamine has been used by Johnson⁵⁷ for the treatment of infantile eczema, with reputedly good results. He employed this preparation in the treatment of eighteen patients with infantile eczema ranging in age from four months to three years. He also included a twenty-three-year-old mother with lesions resembling those of infantile eczema which responded favorably to this treatment. In all cases the orthodox methods of therapy had been tried before treatment with Hapamine was employed.

Johnson's procedure is to do an intradermal skin test with 0.10 c.c. of a 1:10 solution of Hapamine. If this test is negative after thirty minutes, 0.20 c.c. of this same dilution is injected. At the next visit undiluted Hapamine, 0.1 c.c., is given subcutaneously. Injections are given three times a week as a rule although sometimes as often as every four hours. The dose is increased by 0.1 c.c. of undiluted Hapamine at each subsequent visit unless there is an untoward local reaction. There were only a few in the author's experience and none severe. The dosage at which improvement occurred varied from 0.5 c.c. to 2.0 c.c. Once the maintenance dose is reached, the intervals may be reduced to once a week or once every two or three weeks and may sometimes be stopped altogether. If discontinued entirely, some cases have recurrences. The author is obviously enthusiastic about this method of treatment but does not claim that it will cure all cases, and he describes one case where the treatment did not help. He states that the point which the parents stress more than any other is not necessarily the disappearance of the rash but rather the change which comes over the baby. When the treatment is effective, the baby rests better, eats better, and gains weight rapidly.

The use of Anthallan, a drug which has obtained much newspaper notoriety as a cure-all for allergic diseases, in dermatology is discussed by Ereaux and Craig.²⁶ This drug is said to belong to a new class of synthetic organic compounds, the aminized phthalides. Their pharmacological action, is said to be interference with allergic reactions. The drug is supplied in capsules containing 0.085 grams and is administered orally in capsule or in powder form. It may be given, mixed with food, to infants and children. Infants are started with four to six capsules a day, gradually increased to twelve to fifteen. The authors state that no remarkable change can be expected during the first seven to ten days of administration, and the maximum daily dose, six capsules for infants and eight to fifteen for children and adults, should be continued for the second and third weeks and a smaller daily maintenance dose for two to three weeks more.

The drug is slow to clear up objective lesions but lessens itching and consequent scratching and thus helps to avoid the danger of secondary infection. The apparent failure to completely remove or clear the skin lesion reflects on the dermatologist

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rather than on the Anthallan. Combination therapy of Benadryl and Anthallan was productive of prompt results in relieving itching and aiding sleep.

Twelve cases of infantile eczema were followed for an average of 17.5 days. In nine cases there was reduction in itching and in eight the children were observed to sleep better. The primary skin lesions were unchanged. Twelve patients with chronic atopic dermatitis were followed for an average of twenty-four days with somewhat similar results. An eruption following sulfathiazole and one following penicillin were said to have been relieved while on the drug. Anthallan was of no help in miscellaneous cases of chronic urticaria, urticaria pigmentosa, pruritus vulvae, and seborrheic dermatitis. Side reactions to Anthallan were not significant, and the authors conclude that Anthallan is a safe nontoxic drug which is definitely useful in controlling pruritus and allergic dermatoses.

The reviewer gets the impression that there is no evidence presented in this article that Anthallan has any specific anti-allergic action whatsoever. Whatever benefits derive seem to occur from relief of itching. This also occurs when sedatives such as phenobarbital or Demerol are used, and certainly specific antiallergic action is not claimed for these drugs. The periods of observation were also much too short for conclusions to be drawn as to the really effective value of the drug, even as an antipruritic. Many instances have been observed where Benadryl or Pyribenzamine for a short time appear to be startlingly effective as antipruritics but this action is not, unfortunately, constant or persistent in every case although very useful temporarily.

MISCELLANEOUS DERMATOSES

Strickler¹⁰³ has reported an interesting series of five cases of Kaposi's varicelliform eruption, all in children, which apparently indicate the communicability of this disease. The original case was a noneczematous infant who developed this disease with the eruption appearing five days after smallpox vaccination at about the age of two and one-half months. The eruption persisted, and the infant was hospitalized at the age of four and one-half months in very poor condition and died not long thereafter of marasmus. The child had been hospitalized in the dermatological ward with six children with eczema. Of these, four developed Kaposi's varicelliform eruption. Their ages were nine months, one and one-half years, two years and seven years. All made uneventful recoveries. In one of these cases the Paul test was positive. The author states that the evidence presented in his study indicates that the disease is transmissible and also suggests that the condition could be a form of vaccinia.

The reviewer agrees with the author and notes that evidence previously considered in these columns^{43a, b, c} indicates that Kaposi's varicelliform eruption is a virus disease which has in some instances definitely been proven to be due to the virus of herpes simplex. Other viruses, as those of vaccinia, can, however, produce the same identical picture.

Schwartz and Brainerd⁹⁵ described three cases of erythema multiforme in children age fifteen months, seventeen months, and nine years, respectively, with involvement of the skin and mucous membranes following smallpox vaccination. This happens very rarely. They also report three other cases of erythema multiforme, one in an allergic girl eighteen years old, following a sore throat; another case in a woman of twenty-one years following administration of horse serum for scarlet fever, and another in a boy three and one-half years of age, following an upper respiratory infection. In four of the six patients there were lesions of the buccal mucous membrane and to a lesser degree of the conjunctivae. This form of erythema multiforme in which the mucous membranes are involved is called the Stevens-Johnson syndrome. The author states that the occurrence of erythema multiforme following smallpox vaccination, horse serum administration, and during rheumatic fever, together with a high incidence, (50 per cent) of an allergic history, suggests that the disease represents an allergic reaction.

Lichen urticatus is a dermatosis which is very commonly referred to the pediatric allergist. Webster¹¹² has given a very concise and instructive discussion of this condition. He states that it is common in the spring and early summer months in children three to twelve years of age and usually disappears in the early fall. Attacks are apt to recur in following years at the same seasons but become less and less severe and usually disappear by the time the patient is twelve years old. The disorder is more prevalent at times when fresh fruit and vegetables are usually taken freely, and a certain measure of relief is obtained by reducing these foods in the diet. Chocolate, fish, and nuts should also be excluded. Skin testing is of no help though food diaries may be of assistance. Any type of treatment is disappointing. Sedation, keeping the bowels open, and the use of Benadryl or Pyribenzamine sometimes appear useful.

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The primary lesion is a pinhead to pea size urticarial wheal which is most apt to appear in the late afternoon or early evening and which is extremely pruritic. Within twelve hours it becomes transformed into a solid pinhead or slightly larger size deep red hemispherical papule which because of the intense itching is commonly scratched to the point of erosion with subsequent formation of a small, capping crust. Superficial scarring and pigmentation are not uncommon.

This condition is most frequently confused with scabies. In both, itching is severe and usually worse at night, and in both excoriation and secondary infection may play a prominent part. The differential diagnosis is as follows: In scabies the sites of predilection are the flexor surfaces of the wrists; interdigital surfaces of the fingers; the genitalia; the buttocks; and anterior axillary folds. There are never any lesions on the face. In lichen urticatus the extensor surfaces of the extremities are affected and also the face; the genitals are rarely affected. In scabies the primary lesion is a burrow; in lichen urticatus the urticarial wheal, a lesion rarely seen in scabies. Other points are the seasonal occurrence of lichen urticatus and the frequent history of similar trouble at the same season in past years. Also lichen urticatus will not respond to adequate anti-scabetic treatment.

Woringer¹¹⁶ discusses a group of dermatoses of infants, including seborrheic eczema, erythema neonatorum, and erythrodermia desquamativa. He regards these diseases as variants of the same condition which is unrelated to infantile eczema, with which they are often confused. He believes that this condition, which he prefers to call dermatitis of the newborn, is due to an infection with an unknown organism, perhaps a fungus. This disease is contagious and the treatment is that of an infection. Dietary therapy is of no avail. The disease generally disappears in a few weeks or months but may recur. Only the generalized form has a bad prognosis. The reviewer notes that it will require considerable study to confirm Woringer's hypothesis.

Stomatitis and occasionally circumoral dermatitis in children chewing bubble gum has been reported by Ouer.⁷⁰ In a school of approximately 300 children, between ten and fifteen cases were found. Sheldon⁹⁸ reported a case of contact dermatitis of the lips in a girl eight years of age from bubble gum. The reviewer has seen one allergic child in whom bubble gum caused itching of the gums.

BRONCHIAL ASTHMA—GENERAL CONSIDERATIONS

The importance of an early correct diagnosis is stressed by Fisher³¹ of the Royal Manchester Children's Hospital. Of 220 children, 48 per cent developed symptoms during infancy, either spontaneously or as the result of the mild physiological strain of teething. Another 39 per cent had their first attack between the ages of two and six years, often ushered in by some respiratory infection, with measles and whooping cough as the predominating infections. These children often exhibit an inextricable blending of allergic and inflammatory disease known as the "lung damage type of asthma." In 87 per cent of these children, therefore, asthma was manifest before the seventh year of life. The author considers asthma chiefly under three headings: nervous, alimentary, and respiratory. His presentation of the nervous aspects was discussed above under the consideration of psychosomatic problems.

Chest symptoms of unexplained origin in early life should immediately arouse suspicion of allergic disease. Edema appears to play the prominent role in early childhood, leading to symptoms suggestive of inflammatory processes. The spastic element does not characteristically develop until the child grows older. The author states that the spastic type of attack may occur at any age and is characterized by rapid onset and offset. The edematous type is slower to develop and resembles an inflammatory process, often leading to a wrong diagnosis. It is exceedingly important to prevent or modify measles and whooping cough in the asthmatic or potentially asthmatic patient. Fifty-seven children under the author's care had their tonsils and adenoids removed. The results noted at least six months after operation were: in twelve marked improvement was reported; in thirty-six there was no change in the incidence or severity of attack; in six the asthma was said to have been worse; and in three the operation was blamed for the onset of the disease.

The author believes that breathing exercises undoubtedly supply one of the most beneficial forms of therapy in the disease. The steady tendency to diminution in the severity of the attacks and cessation of symptoms for increasingly long periods as the child grows older was noted in the majority of these children. This was particularly true of those developing symptoms in infancy presenting the most uncomplicated form of the disease. Those suffering from the lung damage type of the disease did not show the same promising progress.

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The importance of chronic nontuberculous bronchopulmonary infection as probably the most common disabling pulmonary disease has been emphasized by Finke.³ The presence of such a disease, commonly but erroneously regarded as noninfectious, in other members of the family, as the cause of subacute and chronic pulmonary disease in children under two years of age, is also stressed. Many cases of chronic nontuberculous pulmonary infection in children are probably due to failure of rigorous observation and follow-up therapy in children who have had pneumonia, especially when this occurs as a complication of measles or pertussis. The author stresses the importance of chronic bronchitis as the direct cause of what is commonly diagnosed as asthmatic bronchitis, intrinsic or bacterial asthma or infectious asthma. Suitable therapy, particularly prolonged treatment with penicillin aerosol, by eliminating bronchial infection in the early stages of the disease, may frequently lead to complete recovery and disappearance of the asthmatic symptoms.

Apparently the author completely disregards the development of an allergic constitution as a predisposing factor favoring the development of chronic bronchopulmonary disease, even when this condition appears to be familial, and thus directs his attention to treatment of the resulting infections rather than to a more basic form of prophylaxis. Nothing is said about the relationship of sinus infection or allergic sinus conditions to chronic nontuberculous bronchopulmonary infection. Nevertheless the abstractor feels that Finke has rendered a valuable service to pediatrics in pointing out the beneficial effects of prolonged penicillin aerosol therapy in the treatment of this disease, once established, regardless of the possibility of underlying allergy. Whether or not such treatment as he suggests will prevent the development of chronic nontuberculous bronchial infection will require follow-up studies on large numbers of children after pneumonia, as compared with control groups not intensively treated. It will also be necessary in such a series to note whether or not there is any significant difference in such cases between children with associated allergic disease and those in whom no allergy can be demonstrated.

DIFFERENTIAL DIAGNOSIS OF BRONCHIAL ASTHMA

The inadequacy of the present definitions of the term, "bronchial asthma," is pointed out by Glaser⁴⁰ who suggests the following: "Bronchial asthma may be defined as a form of obstructive emphysema of allergic origin, involving both lungs throughout, characterized by paroxysmal attacks of dyspnea, chiefly expiratory, accompanied by wheezing heard on auscultation of the chest and typically relieved, at least in the early stages of an attack, by sympathomimetic drugs. The pathological physiology consists of edema, increased secretion of the mucous glands, spasm of smooth muscle, and usually a local tissue and fluid eosinophilia." This definition emphasizes the fact that bronchial asthma is only one form of obstructive emphysema, although it is the most common form. All so-called nonallergic asthmas are other forms of obstructive emphysema and should be so designated.

Important differences from adults in the symptomatology of bronchial asthma in infants and children, and a number of diagnostic aids are suggested. The method of eliciting latent asthmatic rales by means of forced voluntary expiration as described by Clarke,¹² a procedure of great diagnostic value, is discussed. The author at that time was not familiar with the technique of Fineman²⁸ devised a number of years earlier, for the same purpose, particularly in pediatric practice. This consists of listening to the chest of an infant or young child (who will very often not co-operate by expiring forcibly) while at the same time manually compressing the chest.

Glaser's paper does not attempt to consider all the diseases which might possibly be confused with bronchial asthma but is limited to those of most importance or most interest to the pediatrician as well as a few which are very rare but with which a specialist in pediatric allergy should have at least some familiarity. The conditions considered are asthmatic bronchitis, foreign body in a bronchus, pulmonary manifestations of cystic fibrosis of the pancreas, thymic asthma, Ayerza's disease, dust bronchitis, sighing dyspnea, bronchotetany, and cardiac asthma. Two cases of cardiac asthma in children eleven and twelve years of age, respectively, are briefly described. These are believed to be the youngest cases yet mentioned in the literature. The importance of radiography and bronchoscopy in case there is any doubt as to the diagnosis is stressed, particularly where the symptoms could conceivably be produced by a foreign body.

BRONCHIAL ASTHMA—TREATMENT

The hope that the overwhelming majority of asthmatic children will ultimately be cared for by the pediatrician and that it will be necessary to consult the pediatric

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allergist only in those cases which do not respond to treatment is expressed by Ratner.⁸¹ He stresses the importance of an accurate diagnosis and urges careful history taking. The child must be studied thoroughly from both the standpoint of pediatrics and of allergy. Multiple sensitivities are the rule rather than the exception. The value of stock vaccine containing a multiplicity of organisms is stressed, the author pointing out that the nonspecific effect of the anamesic reaction in some unknown manner stimulates antibody formation in general. Autogenous vaccines have no particular advantage over stock vaccines. General and specific directions are given for the relief of asthmatic attacks. The author states that it is criminal to give morphine or its derivatives during an attack, and the importance of relieving the patient's apprehension is stressed. In the author's experience Pyribenzamine or Benadryl are of little value in the treatment or prevention of asthma.

In a recent publication, Bowen⁸ has brought up to date his discussion of "Some Practical Suggestions in the Management of Asthmatic Children" reviewed here in a previous issue.^{43c} Among many other practical suggestions Bowen stresses the fact that it is a good plan to bathe the asthmatic child in the morning and not during the late evening. Very often the evening bath produces chilling, particularly in those cases who are prone to perspire excessively. Tobacco smoke and tobacco ashes as nonspecific irritants are also mentioned. It is pointed out that at times a child susceptible to horse dander may acquire asthma from this brought in on the clothes of members of the family who ride or come in contact with horses. A similar situation is present with regard to cow dander. For treatment with house dust injections, Bowen prefers the antigen developed by Dr. B. Efron.*

Salen⁹⁰ reporting from Sweden, presents a preliminary report on eighty-five children with severe asthma. Recovery, almost complete cure, or very marked improvement occurred in seventy-four cases (94 per cent). The methods used were essentially the same as those employed in this country except that his cases were also treated with eucalyptus tar inhalations. The author states that the prognosis is good if treatment can be begun before the occurrence of emphysema, purulent bronchitis, or other complications.

An attempt to systematize the symptomatic treatment of bronchial asthma in infancy and childhood has been made by Glaser⁴⁰ who feels that it is highly important for the pediatrician and general practitioner to have a definite procedure to follow in such cases. It is pointed out that in infants and young children attacks of bronchial asthma may start suddenly without prodromal symptoms. However, particularly in infancy and childhood, prodromal symptoms may occur and these are usually the symptoms of an upper respiratory infection or "cold." The mother may learn that these symptoms may precede the onset of wheezing by several hours, sometimes as long as twenty-four hours or more. Under such circumstances an attempt should be made to abort the impending attack of asthma and this may often be accomplished by the following procedures which are also useful in the treatment of an acute attack of asthma:

1. Put the child to bed.
2. A cough mixture containing ephedrine is started. The author's favorite cough mixture is as follows:

Codein sulphate	0.25 gr. iv
Ephedrine sulphate	0.40 gr. vi
Glycerin	10.0 dr. 2
Syrup of hydriodic acid	
and syrup of cherry aa qs ad	120.0 oz. 4

A teaspoon of this mixture may be administered every three or four hours to a child three years of age and upwards. Proportionate doses may be given to smaller children. The significance of each of the ingredients in the above mixture is discussed. Fluidextract of ipecac may be added if desired, say 0.25 c.c. (3 to 4 minims) in the above mixture.

3. Nose drops containing a mild vasoconstrictor such as ephedrine or neosynephrine should be started. It is of the utmost importance that the drops should be administered with the child in a dorsal (Proetz) or lateral (Parkinson) head-low position.

4. Steam inhalations may be tried unless it is known that steam disagrees with the

*Distributed by Endo Products Company, Richmond Hill, N. Y.

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child or unless the attack occurs in the summertime when steam is of little value except in dry climates.

5. Aminophylline suppositories should be used. A child three years of age will easily tolerate a suppository containing 0.25 gm. (3 $\frac{3}{4}$ grains). If the child is sensitive to chocolate, a base free from cocoa butter should be selected.[†] The action of the suppository may be helped by the addition of a small amount of suitable barbiturate.

6. Ephedrine may be administered orally.

7. If ephedrine does not help, inhalations of epinephrine hydrochloride 1:100 are often most useful. Preparations containing glycerin are preferable.

8. If the foregoing measures fail to relieve an attack, epinephrine 1:1000 should be injected hypodermically. It is important that some member of the family should have been capably instructed in this procedure. It is pointed out that the two most common errors in the hypodermic administration of epinephrine hydrochloride are: (1) too long a delay between the onset of otherwise unrelieved asthma and the hypodermic administration of epinephrine, and (2) improper dosage of epinephrine. The tendency is to use too large a dose. The best dose is the minimum which will accomplish the desired effect because this dose will also minimize the disagreeable side reactions.

In the treatment of status asthmaticus in infants and children, the necessity of hydration is stressed. This is of supreme importance and is very often sadly neglected with disastrous consequences. The single most useful drug in status asthmaticus is aminophylline intravenously. This may be given in a dose of .006 gm. per kg. of body weight (1/20 grains per pound). This is the dose advocated by Pratt,⁷⁵ and it will be noted that it is in proportion to the body weight of the infant, the same dose of aminophylline given intravenously to the average adult (0.5 gm.). Demerol is occasionally useful in this condition. It may be given to an infant or child in the same dose as given to an adult in direct proportion to the body weight of the child.^{43b} It may be administered mixed with the adrenalin in the same syringe. An oxygen tent, provided the atmosphere is kept moist, should be used in severe or prolonged asthmatic attacks without waiting for the child to show clinical evidence of cyanosis. Bronchoscopy must also be considered in cases not responding to the usual methods of treatment.

The so-called antihistaminics, as Benadryl and Pyribenzamine, will occasionally prevent the onset of asthma in some individuals, if given early. They will also undoubtedly relieve mild asthmatic attacks in some instances but they have no value in status asthmaticus and should not be used in this condition because of their tendency to dry secretions.

Ratner⁸³ emphasizes the fact that in some instances of bronchial asthma where the injection of epinephrine fails to give relief, the difficulty may be due to bronchial obstruction rather than to bronchiolar spasm. This may occasionally and dramatically be relieved by the induction of vomiting following the administration of syrup of ipecac. The dose for infants and young children is $\frac{1}{2}$ to 1 teaspoonful, repeated in larger doses as 2 teaspoonsful if the smaller doses do not cause vomiting. For older children and young adults it may be necessary to give repeated doses. The action of the ipecac may be enhanced by following its administration with lukewarm water.

The physiological explanation which Ratner offers for the relief of asthma by the induction of vomiting is most interesting. He states that according to Macklin⁸⁴ there are three mechanisms for the expulsion of material from the tracheobronchial tree: (1) the cough reflex, (2) the action of cilia, and (3) a wave of motion said to resemble peristalsis. These three often work together. According to Gunn,⁴⁶ the cough reflex functions in the upper airway, the cilia act as far down as the finer bronchioles, while "peristaltic" movements evacuate the entire tract, even including the airway terminals. These activities overlap, the upper part of the airway having all three, the intermediate part two, while the terminals would have only one mechanism for evacuation, namely, that of "peristaltoid" motion. This is brought into play only under abnormal condition, such as the ejection of masses of thick exudate from the respiratory lumina. Because of the resemblance of this process to reverse peristalsis in the gastrointestinal tract, it is described by Reinberg⁸⁴ as "tracheal vomiting," a picturesque term favored by Ratner. By this process bronchial obstructions, particularly those due to thick mucus, may be released which under ordinary circumstances might persist for days.

Steam, as used by Prigal⁷⁶ for the production of medicated aerosols, has been discussed in a previous review.^{43c} More recently Prigal, Brooks, and Harris⁷⁷ have

[†]As propylene glycolmonostearate or the glycerin base suppository of the N.F. See reference 43b.

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reported on the use of aminophylline aerosol produced by steam in the treatment of bronchial asthma in adults. Of forty patients with bronchial asthma, thirty-two (80 per cent) were afforded some relief, ranging from slight temporary relief to marked and prolonged relief. Five cases (12.5 per cent) with severe asthma failed to respond to aminophylline by inhalation after failing to respond to aminophylline intravenously. Some cases unresponsive to the aerosol did respond to the intravenous injection; some cases responded to neither method. It would appear that this method of treatment might be particularly valuable for infants and children. However, the general employment of this method awaits commercial production of a special vaporizer.**

Fundamental studies in the electrolyte excretion with various forms of allergy in bronchial asthma have been made by Stoesser and Booth.¹⁰¹ They made metabolic studies in the case of six children with chronic asthma ranging in age from nine to seventeen years. It was found that the ingestion of potassium chloride led to a diuresis which caused loss of sodium from the body. In most instances this was associated with an apparent improvement in the severity of the asthmatic symptoms. On the other hand, the asthma was aggravated by the retention of sodium and the excretion of potassium which occurred with the ingestion of sodium chloride and the administration of adrenal cortex extract and desoxycorticosterone acetate.

DESENSITIZATION IN ALLERGIC DISEASES IN CHILDREN

Brandberg and Wilander⁸ have reported from Sweden on the treatment of allergic disease by the injection of specific allergens. They believe that better results are obtained from allergens prepared themselves and have the impression that all allergens should originate in surroundings not too far removed from those of the patient. Among the unusual extracts which they use are: birch leaves, birch catkins, hazelnuts, boiled as well as uncooked milk, cooked and raw egg yolk and eggwhite, and sawdust. In desensitization, as they term it, they start with the appropriate dilution and continue until the patient is able to tolerate a dose of 1 c.c. of the undiluted extract without local or general reactions. They state that this dosage is generally reached within eight to fourteen days, and thereafter desensitization is continued with one injection of allergen monthly for one year.

The authors report twenty-eight cases, twenty boys and eight girls. No deaths occurred. The great majority of the patients were asthmatic. Five had eczema and urticaria and only one had hay fever. No patients with gastrointestinal allergy were observed. The great majority of the cases, 60 per cent, reacted to Swedish house dust. One-third of the cases reacted to horse, cat and cattle danders. The ages of the patients at the time of treatment ranged from one to twelve years with no one age predominating. It was noted that blood eosinophilia was inconstant.

Twenty-five of the twenty-eight patients studied were reported upon. Considerable improvement was noted in nineteen (76 per cent), and no improvement in six (24 per cent) cases. Deterioration of the condition was not noted in any case. No patients recovered completely. The case of a five-year-old boy with bronchial asthma is reported. He reacted to a number of allergens, notably fish and horse dander. Apparently he was tested intradermally because the authors state that the testing evoked a severe generalized reaction. Without giving details they state that desensitization was carried out. They do not say to what but presumably to horse and fish. It required eighteen days for the preliminary desensitization to be completed. However, they finally reached a dose of 1 c.c. of the undiluted extract, to which the patient reacted with facial edema of short duration and a mild attack of asthma, and thereafter he was given one injection monthly of the extract, and at first even these injections gave rise to transient urticaria. They report, however, that the patient had very good results. They also discussed the case of a two-year-old girl who suffered from severe infantile eczema during her first and second years. When the eczema cleared up, asthma and urticaria appeared, primarily as reactions to fish and eggs. The authors at the time of this report had not completed desensitization which had been under way for four months but state that this had already led to a decided improvement. The authors feel that specific desensitization is useful and should be instituted before the condition becomes chronic.

The reviewer feels that the above report is interesting because it is at such variance with the common experience in this country. Hypodermic desensitization, or "hyposensitization," as it is better termed, is almost never practiced to foods in this country. The feeling among pediatricians, and this is commonly borne out by experience, is that if the child refrains from eating a particular food, he will

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eventually, even though it may take several years, lose his sensitivity to that particular food. Hyposensitization to foods by the method of injection is considered extremely dangerous and exceedingly time consuming, and scarcely worth the risk and effort.

DEATH FROM ASTHMA

Tichenor and Lafsky¹⁰⁶ have reported the case of a three-year-old colored girl who was hospitalized because of wheezing of nine hours duration. The girl had been apparently well except for two brief asthmatic attacks two months prior to admission. The present attack was not initiated by respiratory infection or other evident cause. She became progressively worse and died fifteen hours after admission. The pathological diagnoses at necropsy included: asphyxia due to generalized bronchial obstruction from excessive bronchial mucus, pulmonary emphysema; and right heart failure. Hemolytic staphylococcus aureus had been obtained on throat culture, and culture from the lungs and bronchi grew out Gram-positive diplococci resembling pneumococci, but these could not be typed. The whole picture was that of an overwhelming infection in an asthmatic child.

Since the treatment of severe status asthmaticus in infancy and childhood is an emergency measure which requires proper and rapid action because of the limited reserves of these patients, the reviewer would like to comment upon the type of treatment accorded this child which is considerably at variance from his own practice. It is agreed that such a patient might be benefited by being placed in an oxygen tent. Ratner⁸⁰ disagrees with this because of the alleged drying effect of oxygen on the mucous membranes and the fact that such children often have claustrophobia. However, in my experience, critically ill children seldom seem to worry about claustrophobia, and the oxygen, to avoid drying effect, can be bubbled through a readily available, highly effective special apparatus, or 5 per cent carbon dioxide as an expectorant can be added to the oxygen.

A dose of Adrenalin, 4 minims, a very small dose under the circumstances (7½ minims would have been a good starting dose) was given this patient. This was followed by the injection of Adrenalin in oil, a totally useless procedure under the circumstances. The dosage of Adrenalin should have been repeated with appropriate increases until it was determined whether or not the child was Adrenalin fast, and if she were, the best medication for this condition, aminophylline, should have been given intravenously. The oral administration of Tedral under such circumstances is also a completely useless procedure as was the administration of Benadryl. Benadryl will not help asthma except occasionally to prevent attacks and in some instances to relieve very mild attacks. It has no value in status asthmaticus and may do harm by drying and thickening the secretion.

It would impress the reviewer that in addition to aminophylline intravenously, mentioned above, the child should have been given parental fluids with dextrose, sulfadiazine, and penicillin or streptomycin. Bronchoscopy also appears to have been indicated. Antibiotic aerosol might also have been tried.

THE PATHOLOGY OF ASTHMA

In a very comprehensive article, Gay⁸⁶ has reviewed the literature of the subject of the pathology of the asthma and to this has added a series of twenty-four patients at the Johns Hopkins Hospital who died after a clinical diagnosis of bronchial asthma in which asthma had been recorded as either the primary or secondary cause of death.

In this series were three infants. The first was a white male child who died at the age of six months. Respiratory symptoms had started when the child was three weeks old and asthmatic attacks were apparently definite at the age of two and one-half months, occurring three or four times a day. Allergy was present on both sides of the family. Skin tests by the passive transfer technique were entirely negative. The terminal attack of bronchial asthma was accompanied by bronchitis and bronchiolitis and lasted about three weeks. A tracheotomy following bronchoscopy was performed the day before death, and thick purulent material was found in both bronchi. The anatomical diagnoses following necropsy were: mucopurulent plugs in the bronchi, purulent bronchitis and lobar pneumonia, bilateral and squamous metaplasia of the bronchial epithelium. There was no blood eosinophilia and no specific cause for the asthma other than infection could be found.

The second case was a white female infant, twenty-seven months of age, with a history of asthma beginning at the age of nine months. The child also had eczema. There was allergy on both sides of the family. The child was sensitive both by passive transfer tests and clinically to egg albumin, banana, peanut, and orris. It is

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interesting that the paternal grandfather would develop angioneurotic edema from bananas. The terminal attack started with a cold and the mother gave the child a preparation of banana powder. A severe attack of asthma followed from which the child never recovered. A small dose of morphine was given with apparent relief at first but the child suddenly stopped breathing and died in a state of extreme emphysema. At necropsy the lungs were distended to about two and one-half times normal size. The anatomical diagnoses were: bronchial asthma; obstruction of bronchi by mucus; cardiac dilatation and hypertrophy (right) and emphysema. Blood eosinophilia was not mentioned.

The third patient was a white female child, twenty months of age. The case is particularly unusual because it was the first attack in the life of the child and continued for only two days. The family history was negative for allergy. The illness started with an asthmatic bronchitis. After two days, the patient was admitted to the hospital and that day she developed a fever of 108.6° F., began Cheyne-Stokes respirations and died the following day in convulsions. There was a blood eosinophilia of 1 per cent. The anatomical diagnoses were: bronchial asthma with partial obstruction of many bronchioles; foci of atelectasis and pulmonary edema; and bronchitis.

From these three cases Gay draws several lessons: (1) The prognosis for acutely ill asthmatic children is always serious. Hospitalization is preferable as frequently dehydration requires intravenous fluids. (2) Even small doses of morphine should be avoided. (3) Bronchoscopic aspiration of mucus is indicated even in infancy but it is impossible to dislodge mucus from distant bronchi.

The reviewer would like to add also that these cases, since they are always apparently accompanied by infection, should be early and vigorously treated with appropriate sulfone compounds and antibiotics, which is yet another reason for early hospitalization. The cases reported by Gay occurred before such treatment was possible, and it is probably significant that no further deaths from asthma have occurred in this age group in his hospital since the advent of such therapy, at least until the time of his report.

A discussion by Unger¹⁰⁸ of five deaths from bronchial asthma includes the case of one colored girl, a year old, who was known to have had asthma since the age of three months. She entered the hospital in a severe attack, failed to respond to therapy, and died five hours after admission, seventeen hours after the onset of the attack. The important pathological findings were limited to the lungs which were emphysematous and felt doughy throughout, and greyish yellow mucopurulent material could be expressed from the smaller bronchi. Microscopically there was hypertrophy of the muscles of the bronchial walls and infiltration by large number of eosinophils, confirming the clinical diagnosis of bronchial asthma. *B. coli* was reported on culture.

BENADRYL AND PYRIBENZAMINE

The use of Benadryl in the treatment of certain allergic diseases of children is reported by Logan,⁶⁸ who studied its use in seventy-one children. The average daily dose varied between 0.5 to 6 mg. per pound (1 to 12 mg. per kg.). A daily dose of 2 mg. per pound (4 mg. per kg.) was frequently effective. The longest any child in this series took the drug was nine months. No ill effects were observed in this particular case. Undesirable side reactions, of which the commonest was drowsiness, were noticed in about one-quarter of the cases (24 per cent). The drug had to be stopped in only six of these seventeen cases. Hematuria was noted in one three-year-old boy, and the Benadryl was discontinued on that account. The author states that Benadryl may be prescribed along with potassium iodide, sodium iodide, epinephrine, aminophylline, and diphenyl hydantoin sodium (Dilantin). Good to fair results were obtained in nineteen of twenty-one cases of bronchial asthma. Good results were obtained in ten out of thirteen cases of hay fever and ten out of eighteen cases of vasomotor rhinitis. Only one of sixteen children with urticaria failed to respond to Benadryl.

A thorough review of the subject of Benadryl, Pyribenzamine and other so-called antihistaminic drugs in the treatment of allergy is given by Ratner.⁶² He states that from their mode of action it is obvious that these drugs can act only as palliative agents and do not eliminate the basic mechanisms responsible for allergic symptomatology. One of the effects of these drugs is the clouding of judgment, and this has serious potentialities. A child who runs out into the street after taking the drug, with judgment gone, might be easily run over. An individual in swimming might conceivably be so overcome by drowsiness as to drown. The author states as follows: "Much as we would desire it, I cannot conceive of a universal cure-all in allergy. The very nature of allergy and its underlying anti-

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gen-antibody mechanisms preclude it. Were we to discover how to prevent the development of allergic antibodies, the problem would be settled. But the essence of allergic antibodies is the very essence of all antibodies. A substance that would destroy all antibodies would obviously lead to a state incompatible with survival against noxious invading substances. The body must continually manufacture immunizing agents. The amelioration of allergy is based on the ability of the body to produce enough antibodies so that they may eventually reach the circulation and act as blocking and neutralizing bodies. Allergy is an ever present battle against all types of foreign substances inhaled, ingested, or injected."

A considerably more enthusiastic report on the use of Benadryl is made by Goldstein.⁴⁴ He reported the findings in seventy-nine allergic patients treated with Benadryl, of whom seventy-one were children and eight adults. The age range in the children was two to sixteen years and in the adults from nineteen to thirty-five years, with their sex about equally distributed. The favorable responses to Benadryl administration show 76 per cent of all groups have excellent improvement, 10 per cent good, 6 per cent fair to poor, and 8 per cent no improvement.

Goldstein reports that the addition of pyridoxine hydrochloride, 25 mg. added to each dose of Benadryl, would cause the drowsy feeling to wear off. This also diminished nausea, vertigo, and diplopia although these side reactions occurred but rarely. In two patients in whom pyridoxine hydrochloride did not remove the secondary effects, 50 mg. of niacinamide were given and the side effects of vertigo and nausea were immediately relieved.

A very interesting unusual side effect from Benadryl which occurred in a three and one-half-year-old boy is reported by Weil.¹¹³ Because of pollinosis, 50 mg. of Benadryl had been administered twice a day. This dose gave good, although not complete, relief. On one occasion, at night, to alleviate severe sneezing, he was given a single dose of 100 mg. of Benadryl. Within about twenty minutes he was found sitting up in bed, singing and laughing, and starry eyed, and in general "acting as though he were drunk." At this time muscular twitchings of the face and involuntary spastic movements of the extremities were noted, followed by urinary incontinence, and the child became irrational. He threw himself out of bed, head first onto the floor, but laughed when he was picked up. Seconal 1.5 grains (0.1 gm.) was administered orally, and though the child fell asleep, the muscular twitchings and athetoid movements continued and his speech in moments of wakefulness could not be understood. It was not until about sixteen hours later that the child appeared to be again normal. Subsequently he was found to be able to continue to tolerate 50 mg. doses of Benadryl but larger doses were not tried.

The possible effects of the antihistaminic drugs on the infant *in utero* and at the breast are extremely important but there are very few reports in the literature concerning this. Davidson²⁰ has had two pregnant women whom Benadryl made sleepy and also appeared to stop the fetal movements; in other words, the baby apparently went to sleep also. When the drug was stopped, the movements of the child began again, and there were no untoward effects so far as one could tell. Similar cases have been observed by Glaser.⁴² Ratner⁸² has mentioned a case in which Benadryl, taken every three hours by a nursing mother to relieve contact dermatitis, apparently caused lethargy and constipation in her breast-fed infant five-weeks old.

EPINEPHRINE POISONING

Hanzlik⁴⁹ has rendered a significant service, particularly to allergists, by calling attention to the article by Möller⁹⁸ on the subject of the treatment of acute epinephrine poisoning. Hanzlik states that serious accidents from overdosage of epinephrine would appear to be uncommon and in most instances are probably never reported. These are more likely to occur with accidental intravenous injections than by other methods of administration, but little, if any, attention has been given to possible measures for relieving symptoms. Since the introduction of 1:100 epinephrine for inhalation, the possibility of accidents from the injection of epinephrine have increased. This is particularly true in other countries where the likelihood of difficulty is even greater because solutions of epinephrine ten to twenty times stronger than the solution permitted for use as vapor in this country may be obtained.

Möller of Copenhagen has reported the successful treatment of a child who had been given what is ordinarily a fatal dose of epinephrine. The principle of the procedures used in treating this case should be valuable in mitigating severe symptoms of accidental poisoning from smaller doses. The essential feature was

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prompt and persistent treatment with drugs of the nitrite group. Carbaminoylecho-line (Doryl), a parasympathotropic stimulant used to restore autonomic imbalance caused by the sympathetic overstimulation of epinephrine was ineffective.

Möller's case was that of a twelve-year-old girl whose weight was 34 kg. (74½ pounds), who was given subcutaneously, by accident, 20 mg. of epinephrine, 0.2 c.c. of a 10 per cent spray-solution, equivalent to 20 c.c. of the usual 1/1000 solution of epinephrine, which is double the known fatal dose for an adult man. Nausea, vomiting, and a barely perceptible pulse quickly resulted. Marked general paleness with coldness of the extremities and increased heart rate and blood pressure were present in twenty minutes and unconsciousness in forty minutes. Following inhalation of the vapor from four ampules of amyl nitrite, consciousness was regained without change of blood pressure and heart rate. From then on, the administration of the longer acting members of the nitrite group was pushed during a period of one hour and forty minutes. Nitroglycerin, 3.0 mg., was given at one hour and fifteen minutes, then erythrol tetranitrate, 5.0 mg. by mouth, followed by three doses of 5.0 mg. each intravenously ten minutes apart, followed again fifteen minutes later by another 5.0 mg. intravenously, making a total of 25 mg. of erythrol tetranitrate within one hour and forty minutes after the accident. Three hours and forty minutes after the epinephrine injection, the skin of the face was pink but the legs were still cold and pale. Blood pressure was reduced and thirst marked after the third dose of erythrol tetranitrate; flushing was marked after the last dose.

The recovery of this child from twice the fatal dose of epinephrine is attributed by Möller to the persistent use of nitrites as peripheral vasodilators: these are known antagonists of epinephrine. Other vasodilators, i.e., acetylcholine and aminophylline, have been used in combating epinephrine accidents but have less to recommend them than the nitrites. According to Möller, the aim should be to overcome the marked vasoconstriction so as to improve cerebral circulation and restore consciousness. Möller recommends giving inhalations of amyl nitrite (3 drops) vapor as quickly as possible, followed by a larger dose (2.0 to 4.0 mg.) of nitroglycerin by mouth and then erythrol tetranitrate in divided doses of 5.0 mg. to a total of 20.0 mg. intravenously to control the high blood pressure and promote recovery according to individual requirements. The site of the injection of the epinephrine may also be excised if necessary.

The reviewer notes that an immediate emergency measure which may be used in the case of subcutaneous injections is the placing of a tourniquet above the site of injection of the epinephrine and releasing this at intervals, just as is done in preventing severe pollen reactions when an overdose is inadvertently administered.

BUTANEFRINE

This drug is also known as ethyl-nor-adrenaline or ethyl-nor-epinephrine. Under the latter name it is reported upon by Bubert and Doenges.⁹ It is a sympathomimetic amine which in typical cases causes bronchodilatation but does not raise the blood pressure and stimulates the central nervous system little if at all. In doses of 1 to 4 mg. (average dose 2.4 mg.) injected intramuscularly, the drug gave good relief from bronchial asthma in adults. Routine intravenous use of the drug in doses of 1 to 10 mg. (average dose 2.4 mg.) has also been found satisfactory. This was followed by an average drop in systolic blood pressure 16 mm. compared with 7 mm. following intramuscular administration. In five cases the drug was successful intravenously after aminophylline intravenously and epinephrine intramuscularly had failed to give results. Reactions occurred but were in no instance alarming. These consisted of nervousness, fainting, and erythema. In children an initial dose of 0.5 c.c. to 0.8 c.c. of solution (2 mg. per c.c.) was given intramuscularly, depending upon the age of the child. Occasional nervousness was overcome by reducing the dose by 0.1 or 0.2 c.c. One child seven years of age with severe status asthmaticus was given 0.5 mg. in 10 c.c. of normal saline intravenously, with satisfactory relief. A child eighteen months of age with severe asthma who did not tolerate epinephrine well was given 0.8 c.c. intramuscularly with good results. This was so much more satisfactory in this instance than Adrenalin, because the Butaneprine did not excite the child, that the parents could not be persuaded to use epinephrine again.

For intramuscular injection the drug is supplied in 1 c.c. ampules containing 2 mg., and for intravenous injection in 20 c.c. ampules containing 2 mg. The authors make the point that when the drug is first tried it should be on cases in which one would ordinarily use epinephrine, as well as in cases where epinephrine might have failed. The drug appears to be particularly useful in children because of its low toxicity and lack of stimulation of the central nervous system.

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The reviewer has had a fair experience with this drug and finds it very useful in infants and children because of its effectiveness and lack of side reactions. It has not been found, however, as effective in controlling severe asthmatic attacks as epinephrine. The drug is also useful in older individuals who are sensitive to epinephrine although not every individual who is sensitive to epinephrine will tolerate Butanefrine.

ALLERGY OF THE RESPIRATORY TRACT

Rosenberger⁸⁷ disagrees with the commonly made statement that infection interferes with the development in size of the paranasal sinuses except in rare instances. He quotes the work of Maresh and Washburn⁶⁸ who conclude that there is no definite correlation between the size of the sinus and the amount or frequency of infection in that sinus as evidenced by the roentgenogram. He further concludes that the size and pattern of growth of the sinuses is as much an inherent individual characteristic as the shape of the nose or the color of the eyes.

In a series of 163 patients, Rosenberger noted the great variability of the size of the frontal sinuses in the same individual as contrasted with the uniformity in size of the antrums. However, infection occurred much more frequently in the more symmetrical antrums than in the more variable frontals, a situation one would not expect to find if sinus development were more closely related to sinus infection.

Rosenberger also called attention to the work of Dyke and associates²³ which illustrates the fact that other factors than infection play a role in sinus development. In a small series of patients with infantile hemiplegia, there occurred excessive pneumatization of the ethmoids, mastoids, frontals and petrous tips on the same side as the brain atrophy. The surmise is that this occurs in order to increase the bulk of the skull at the site of the brain atrophy.

A contrary opinion is expressed by Johnston⁵⁸ who states that infection of the sinuses during their period of development has a very definite influence on their normal growth. However, he gives no statistics or reports any special studies to support this opinion. Johnston quotes the report of Ebbs²⁴ in England who found nasal sinus disease at autopsy in 30.6 per cent of 495 children under fourteen years of age in whom death was due to a variety of causes. Of the 152 cases with sinus infection, the maxillary antrum was most frequently involved (29.15 per cent) and the sphenoids next (15.4 per cent) and the ethmoids least of all (13.75 per cent). The reviewer notes that this is certainly contrary to experience with children in this country where the ethmoids appear to be infected far out of proportion to any other of the sinuses.

The ethmoids reach considerable development by the age of two years; the sphenoids attain significant size by three years; and the maxillary antrum, present at birth, is well developed by the age of seven years. The frontal sinuses, fully developed by the age of twelve to fifteen years, are rarely of clinical significance before the eighth or ninth year.

The principal symptoms of sinusitis are nasal discharge, repeated colds, mouth breathing, cough, and cervical adenitis. Other prominent symptoms are: an unexplained daily rise in temperature, poor appetite, inability to gain weight, headache, hoarseness, otitis media, conjunctivitis, blepharitis, and orbital cellulitis.

Allergy is very important in sinusitis, and to treat the sinus infection without regard to the underlying allergy is almost a waste of time. Various methods of examination and treatment of the sinuses are described. An adequate supply of vitamin A in the diet is probably important. Hypothyroidism may also be a factor. A change of climate will also sometimes benefit when all other measures have failed. Sinusitis with an excessive amount of secretion does better in Arizona; where there is not much secretion and the patient feels better on damp days, Florida is preferred; Southern California is best suited for children who have most of their symptoms in the winter months in the northern states. The best climate is fifty or more miles in from the coastline. Radical sinus surgery is rarely necessary in children.

Chronic cough is one of the most troublesome symptoms occurring in childhood, especially in allergic children. Bowman⁶ has made an interesting study of this problem. He states that there is a definite seasonal variation, most chronic coughs being more prevalent and severe during the winter months. Infection of the paranasal sinuses, though commonly overlooked, frequently causes chronic cough in children and the syndrome is known as sino-bronchitis. The sinuses may be infected at any stage of their development, even during the newborn period. Because of the order of development of the sinuses, in general it may be said that the ethmoid and maxillary sinuses are most commonly infected in children; next in importance are the sphenoids; and the least important, the frontal sinuses, which are not likely to be infected in a child eight years of age or less.

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Exposure of the nasal mucous membrane to virulent organisms in experimental animals will always produce sinusitis, regardless of the condition of the animal. It is quite likely that the same thing occurs in children coming in contact with virulent organisms. It has been proven conclusively that stasis in nasal secretion causes infection. Anything which causes edema of the nasal mucous membrane may result in sinus infection. So may other abnormalities which result in defective drainage of the sinuses. Nutritional disturbances also predispose to infection, and in this respect it is interesting that the deficiency of vitamin A is apparently a factor, at least in experimental animals. There is also an allergic sinusitis. The author states that the most important etiological factor in nasal sinusitis is infection of the neighboring lymphoid tissue. Diseased tonsils and adenoids and lymphoid nodules of the nasopharynx act as foci of infection, from which bacteria spread by the subepithelial route to the sinuses.

Infected sinuses contaminate the bronchial tree and produce bronchitis by three possible routes: (1) by postural drainage through the pharynx, larynx, and trachea; (2) by direct extension because of the continuity of the membrane surfaces, and (3) by the mediastinal lymphatics. These routes are at times reversible. In the diagnosis of sinusitis, roentgenograms are essential for they indicate the development and size of the sinus in question. As regards treatment, the author states that among other procedures the judicious use of vasoconstrictors in infections of the nose will promote adequate drainage and prevent stasis. However, abuse of these preparations should be discouraged. In the treatment of chronic sinusitis if there is an allergic factor, it must be eliminated. Infected tonsils and adenoids should be removed. Any conditions blocking the sinuses ought to be corrected. Nasal drainage must be present if chronic sinusitis is to be cured. A review of Bowman's ideas regarding the treatment of sinusitis by roentgen therapy will be given below.

Van Dishoeck¹¹⁰ has made a study of allergy in children with ear, nose and throat complaints in Amsterdam, Holland. The largest number of patients with nasal allergy occurred at fourteen years. Boys predominated. In thirty-five of fifty cases of definite nasal allergy there were accompanying bronchial asthma or asthmatic bronchitis. The authors agree with Hansel and Chang⁸⁷ that the indications for adenotonsillectomy are the same in the allergic as in the non-allergic individual. Allergic rhinitis and bronchial asthma are not per se indications for this operation.

The hereditary factor did not appear to be important in nasal allergy. Multiple sensitivity was the rule. Inhalants appear to be more important than foods. Absence of eosinophilia in the nasal secretion does not exclude allergic rhinitis. Blood eosinophilia was found to be quite constant, and in only six of the fifty cases was the percentage under 5. Nasal polyps were present only in one case; they do not occur nearly as frequently in children as in adults. The number of leukocytes was also increased. Allergic therapy does not help if organic defects are not corrected and purulent sinuses drained.

Among 500 cases in children three to fifteen years of age, sixty-five patients with suspected nasal allergy were selected. Among these sixty-five were fifty who showed positive skin tests. Only three uncomplicated cases of pollinosis were found. Skin reactions occurred in this order of frequency: house dust, 26; pollen, 23; feathers, 19; seaweed, 9; tobacco, 9; mites in kapok, 8; cosmetic powder, 8; tea, coffee, chocolate, 8; fruits and vegetables, 8; epidermoids, 7; alprgrass, 7; meat and fish, 7; wheat, 5; wool, 4; egg, 3; milk, 2; and pyrethrum, 2. House dust hyposensitization and removal of other allergens was often helpful.

RADIATION THERAPY OF THE LYMPHOID TISSUE OF THE UPPER RESPIRATORY TRACT

Radiation therapy of the lymphoid tissue of the upper respiratory tract to eliminate this type of tissue as a possible source of infection has been discussed in a previous review.^{43c} The use of this procedure is gradually becoming more widespread. Since then, Gay⁸⁷ has discussed the history of the development of the use of radium by Crowe^{15,16} and his associates for treating hypertrophied lymph adenoid tissue of the nasopharynx not susceptible to surgical removal. This was designed, originally for the particular purpose of treating tissue around the internal ostia of the eustachian tubes whose presence caused deafness by occluding the internal ostia of the tubes. For this purpose such treatments have been highly successful. In a study of 795 school children between the ages of eight and fourteen years, it was found that 75 per cent had a marked recurrence of adenoid tissue of the nasopharynx, not because of poor surgery in the original operation but because of the tendency to lymphoid tissue to recur in the mucous membranes.

In the process of removing this tissue by radium it was observed that some of

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these children who were deaf also had bronchial asthma and had failed to respond to the usual methods of treatment. These children had a history of recurring colds associated with asthmatic attacks. Their nasal pharynx contained numerous islands of infected adenoid tissue and it was observed* that after treatment with radium (because of deafness) in many cases there was marked relief of the asthma. The beneficial effect may be due to reduction in secretion, to a decrease in the local absorption of allergens or to the removal of nasal pharyngeal foci of infection. In children with asthma apparently related to infection, nasopharyngoscopic study is definitely indicated.

Ward, Livingston, and Moffet¹¹ have reported a series of thirty-four patients, two to fourteen years of age, twenty-five boys and nine girls. Of these, sixteen had had a previous adenotonsillectomy. In most instances asthmatic symptoms had persisted for more than two years. Twenty-seven of these children had asthmatic attacks after every respiratory infection. All had masses of lymphoid tissue demonstrated by the nasopharyngoscope, even those who had a previous removal of the tonsils and adenoids. Treatment of each child consisted of 2 gram-minutes of radon to each side of the nasopharynx once each month for an average of four treatments. The lymphoid tissue disappeared completely in twenty-three of the twenty-four cases. Following the radon irradiation, many children complained of sneezing and nasal discharge for twelve to forty-eight hours after exposure. In a number of children, asthmatic attacks, sometimes severe, developed after the first or second irradiation.

All forms of asthma were represented. Sixty-eight per cent of the patients obtained from total to 50 per cent relief; 32 per cent obtained no relief. The treatments were helpful or failed to help regardless of whether the asthma was extrinsic or intrinsic. The authors believe that the radon has a beneficial effect other than reduction of foci of infection but the mechanism of this is not yet clear.

According to Crowe and Walzi,¹² the action of radiation is confined to the cells and germinal centers. A few days after irradiation a cell shows chromatolysis and fragmentation of the nuclei. Since the life span of the mature lymphocyte is only a few weeks, the mass of adenoid tissue gradually shrinks because there is no replacement in the damaged germinal centers. The authors prefer the use of radium. They state that they have never had any burns or other serious reactions. Usually three to five treatments at ten-day intervals are required. No treatment should be given during the acute stages of a cold as there is danger of aggravating the cold or causing otitis media. In many instances where it is not possible to operate on children to remove tonsils and adenoids, radiation treatments usually produce results which are as good or better than those of operation alone. The treatment of lymphatic hyperplasia by this method, in children with bacterial allergy causing asthma, has produced very encouraging results.

Proctor⁷⁸ gives these reasons why the surgical removal of the adenoids is not always a satisfactory procedure: It is almost impossible to eliminate surgically all the nasopharyngeal lymphoid tissue. Radical attempts at total surgical adenoidectomy may result in damage to the eustachian orifices. Even if all lymphoid tissue could be removed, the mucous membrane which grows in over the denuded nasopharynx contains lymphoid tissue as an integral part of its stroma. The minutest nodules of lymphoid tissue are capable of growing rapidly to large size under the stimulus of infection or of allergy. Even small remnants of lymphoid tissue may serve as foci of infection.

The indications for and the preliminary treatment to radiation therapy for the removal of adenoid tissue are as follows: Infected or enlarged adenoids as seen by electro-nasopharyngoscopic examination are definite indications. Chronic infection of tonsils or sinuses must be treated simultaneously with, or cleared up before, radium therapy. Severe allergy should be properly handled during or before therapy. When the tonsils are infected, or there is a large mass of adenoids, and the rapid elimination of adenoids is desired, radiation should be preceded by tonsillectomy or adenoidectomy or both. Treatments should not be given during acute infections of the upper respiratory tract. Deafness apparently associated with obstruction of the eustachian tubes is a clear indication for treatment. Chronic infection of the ear, recurrent acute infection of the ear, recurrent acute infection of the sinuses, recurrent acute infection of tonsils (associated with preceding nasopharyngitis), recurrent acute colds, postnasal discharge without other cause, are all usually amenable to this type of treatment. Mouth breathing due to obstructive masses of adenoids will subside when breathing space is restored. Bronchial asthma, though to be wholly or partly on an infectious basis, and especially when

*By Ward¹¹ working in Crowe's Clinic.

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attacks are preceded by infection of the upper respiratory tract, is usually greatly helped.

As indicated in a previous review,^{48c} there are some who prefer the use of the roentgen ray to radium or radon for the treatment of hypertrophied lymphoid hyperplasia of the pharynx. The number of individuals favoring the roentgen ray technique appears to be rapidly growing. If this method of treatment proves to be as effective as radium or radon, there is little doubt that it will replace the latter in this form of treatment. The reasons are obvious. The employment of radium or radon requires a highly skilled operator; it may be a difficult technical procedure in small children and is not without danger. On the other hand, any skilled roentgenologist can successfully administer the proper roentgen therapy. A symposium on this subject was held by Rosenblum, Pearlman, and Uhlmann.⁸⁸ They were interested not only in therapy of the adenoids but also of the tonsils. In Rosenblum's experience there are two forms of hypertrophy of the tonsils: that in which all the anatomic structures of the tonsils become more or less hypertrophied, and that in which the crypts become distended by secretion. Soft tonsils with wide open crypts have offered the best results in Rosenblum's experience, whereas large pedunculated tonsils did not respond as well. Yet he feels that this method of therapy has passed the experimental stage and offers the following advantages: the tonsils are preserved; the entire infectious area is attacked; no anesthesia is necessary; there is no danger of shock or hemorrhage; no local infection can follow the procedure; usually no pain is produced by the treatment; there is no impairment of hearing; no disability follows; and finally treatment can be instituted even in the presence of cardiac or pulmonary pathologic conditions. It is felt that only the tissue that functions poorly, if at all, is destroyed.

The most favorable group for treatment consists of children one to six years of age. Children with tonsillitis recurring every two to four weeks often went for one or more years without exacerbations. Improvement in health was comparable to that following tonsillectomy. Subsequent surgical operation of irradiated tonsils offered no more difficulty than in cases where the tonsils had not been irradiated.

Continuing this symposium, Pearlman, a nose and throat specialist, agrees that there are definite indications for irradiation therapy as opposed to surgery. However, he feels that the pediatrician should be the guide to the treatment of choice. The radiologist, Uhlmann, believes that the roentgen ray is the simplest and safest method of administration of irradiation for the conditions under question. During the past seven years in the Tumor Clinic of Michael Reese Hospital, more than 1,000 patients have received roentgen therapy for recurrent colds, throat infections, cervical lymph adenopathy, impaired hearing, and other symptoms associated with enlargement of the tonsils or with the existence of hypertrophic lymphoid tissue in the pharynx. It is seldom that more than three visits are necessary. In the past five years 600 patients have been treated, of whom 480 could be traced and checked satisfactorily. Of this total, 42 per cent were less than five years of age and 76 per cent less than ten years of age. In this age group the chances for spontaneous improvement without therapy are much less than in the group from ten to fifteen years of age, and since improvement was considered due to irradiation therapy only when the change took place within a reasonable time (four to six weeks) following treatments, it is believed that the factor of spontaneous improvement did not materially influence the results.

Bowman,⁶ whose work on sinusitis as a cause of chronic cough in children was discussed above, has under treatment a series of children with chronic coughs who have virulent infections involving the ethmoids, and the maxillary sinuses who are being treated with roentgen therapy. In nearly all of these cases, conservative measures as local medication, sulfonamides, and cough mixtures had failed. In a series of twenty-five cases of purely infectious sinusitis, allergic sinusitis being excluded, about 90 per cent of the patients have been cured of their nasal symptoms and cough; another 5 per cent have been improved. Follow-up x-rays and examinations in the cured and improved cases have shown clearing of the sinuses and disappearance of the thickened membranes. The lymphoid hyperplasia in the nasopharynx subsided. Generally these patients have increased appetites, gained weight, and possessed more energy. Needless to say their chronic cough has subsided. The parents are enthusiastic about such a form of treatment because it is painless and produces results. The dosage is so small that damage to nasal structures is unlikely to be incurred. An outline of the author's treatment is given.

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COMPLICATIONS OF POLLEN THERAPY

Horesh⁵⁶ reports the case of an eight-year-old girl who was being treated by injections of pollen extract because of ragweed asthma. The doses were gradually increased and after the eighth injection, the mother reported that the child had a convulsion about four hours afterwards. It was felt that the injections had nothing to do with the convulsion, and epilepsy was suspected. The following week the dosage of ragweed was increased and again within four hours the child had a convulsion more severe than the previous one, this time becoming unconscious. Treatments were then discontinued. During the five-year interval which followed there had never been a recurrence of a convulsive attack. Horesh believes that this child was very sensitive to ragweed and was grossly overtreated, convulsions occurring as a result of this.

Jones, Lowance, and Matthews⁵⁹ mention the case of a woman who was given pollen injections while nursing her infant. She reported that on the days she received the injections, after the following nursing, the baby sneezed extremely. This was interpreted by the authors to mean that the child was sensitive to the extract which must have been excreted into the mother's milk in order to produce this reaction.

PROPHYLAXIS OF ALLERGIC DISEASE

Roberts,⁸⁶ a layman, quotes various pediatric allergists as having made the statement in a round table discussion at the ninth annual meeting of the American Academy of Pediatrics to the effect that "Fifty per cent of the allergic cases in the nation may be avoided by stressing certain preventive measures which parents can take." The reviewer feels it is unfortunate that such a dogmatic statement should have been made in a journal intended to inform laymen on the progress of medicine, since there is no scientific evidence whatsoever of the truth of this statement. There is at present only presumptive evidence that allergy may be prevented by use of certain measures which are very reasonable and should be carried out because of this and the equally important fact that they can do no harm. This subject was first brought to the attention of physicians with respect to asthma by Peshkin⁷³ and to allergy in general by Glaser and Landau.³⁹ Since then, further suggestions have been made by many others. Roberts presents these in an interesting and somewhat tabular manner which does not easily lend itself to abstracting. Among the more important suggestions are the avoidance of dietary indiscretions as overindulgence in any one food, especially seasonal and bizarre foods, and the use of foods which have been at least allergenically denatured in part by the use of heat. Women during pregnancy should eat a well balanced diet without overindulgence in any particular food. Overexposure to house dust and pollen is to be avoided as is excessive treatment with drugs, ointments and serums.

ALLERGY AND CLIMATE

The notable contributions of Baker with respect to the influence of altitude on allergic diseases in children have been previously reviewed in these columns.^{43b} In a more recent communication⁴ the author gives two illustrations of her observation that allergic reactions are more common and more severe at high altitudes (Mexico City—elevation 7,434 feet) than at lower altitudes. One was the case of a girl who, starting at the age of four months, would have hives associated with loose bowel movements while in Mexico City. These symptoms always disappeared at lower altitudes, to reappear whenever she returned to Mexico City. This difficulty could be avoided if cow milk, raisins and bacon were omitted from the diet. These foods were well tolerated at lower altitudes except when taken in excess. Another girl, first seen at the age of four years, developed numerous allergic manifestations on coming to Mexico City, particularly urticaria and allergic rhinitis. These could be controlled by elimination diets, milk being the principal offender.

Baker has found that skin tests are not of great value in these cases. Symptoms are generally controlled by eliminating the foods which most commonly cause trouble in Mexico City—egg, chocolate, orange, milk and wheat. With the elimination of the offending foods for a considerable period, sensitivity is generally lost but builds up again on resumption of these foods, usually in a fairly constant time. In Baker's practice, allergic reactions are as common as infections, except in the very poorer groups. The babies begin to develop food intolerance at seven to eight months starting with diarrhea followed by vomiting, allergic rhinitis and bronchitis. Urticaria and eczema are also common. Mexican physicians call the condition "altitude urticaria" and state that the babies will outgrow this.

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Feeding schedules for infants and young children cannot follow those recommended in the United States. Eggs cannot be given every day as is a common practice at lower altitudes. Breast-fed babies in the better classes in Mexico City have greater advantages over artificially fed infants than recorded in the United States. It is not unusual, however, for the breast-fed baby to be allergic to some food in the mother's diet. Under one year, if the child becomes allergic to cow milk, success may be had with one of the following: Nutramigen (if the reaction is mild), burro's milk, and goat's milk, if the allergy is to a specific lactalbumin and not to casein. Soybean milk is not tolerated for more than three or four weeks without causing sensitivity. After a year a much more varied diet can be given, and the more varied the diet, the better off is the child.

In a brief communication to the Paris Pediatric Society, Anglade¹ states that while at the Lafayette Preventorium in Haute-Loire, France (elevation 800 metres or 2,625 feet), he studied the relationship between asthmatic attacks and variations in barometric pressure, the direction of the wind and other meteorological factors. His material consisted of two years observation on eighty asthmatic children. His conclusions were that the frequency, duration and course of the attacks appeared in no way influenced by these factors. The reviewer notes that since this is contrary to common opinion, further work in this direction would be welcome.

FOOD ALLERGY

McGee⁶⁶ studied the incidence of food idiosyncrasies in 150 well babies who came in monthly for their regular routine examinations, and feeding instructions. The mothers were asked to watch for any unusual or abnormal signs and symptoms following the ingestion of the new food or vitamin and then to report it at once, if severe, or later at the next regular monthly visit. No cases were considered which came in for an allergic study, and no skin testing was done. Only one new food was allowed at a time at intervals of three to five days, and mixed foods were avoided. All the infants were under one year of age. Symptoms of food disagreement were classified as: colic, loose stools, eczema, excessive regurgitation, papular rash, constipation, mucus in the stools, vomiting, anal excoriation, abdominal pain, excessive crying, croup, diarrhea, food passed as ingested, head colds, gagging, convulsions, excessive fretfulness, shivering, shock, coughing, erythema, restlessness in sleep, extra stool, hives, flatus, sneezing, and a group listed as "symptoms not described." The foods which disagreed were in the order of their frequency: orange juice, cow's milk, casein, spinach, ascorbic acid, mixed cereal, prunes, tomatoes, cod liver oil, carrots, oats and wheat. Egg yolk disagreed next after wheat. No eggwhite was permitted until after a year of age. It was noted that ascorbic acid was tolerated twice as well as orange juice.

Food dislikes were found not to parallel food which disagreed, but according to McGee a food which is persistently disliked should probably best be avoided. The foods which were disliked in the order of frequency were: spinach, green peas, beets, white potato, carrot, green bean, asparagus, oat, rice and tomato.

The reviewer feels that it would be exceedingly difficult to prove that all the symptoms mentioned above were definitely due to food allergy. There are many other factors which conceivably could produce such symptoms. Probably also, it is not completely fair to assume that the boiling or heating of milk renders the lactalbumin completely innocuous so that the symptoms due to milk ingestion may be attributed to the casein. It also was not stated whether crystalline ascorbic acid or ascorbic acid in propylene glycol was used, and as has been pointed out previously,^{48a} one must consider excipients used along with ascorbic acid in the form of tablets, capsules, et cetera.

According to Chobot¹⁰ gastrointestinal allergy is most frequently seen in the child up to the age of five years. Ninety-eight per cent of food-sensitive children lose their sensitivity spontaneously by the time they are five or six years old and without any type of therapy. The most common foods at fault are milk, egg, and wheat. Many children give positive skin tests to wheat but can eat wheat without trouble. In such cases the possibility of wheat causing trouble as an inhalant rather than as a food should be seriously considered. As regards milk sensitivity, the child may or may not be sensitive to milk but may be sensitive to foods conveyed by the milk, whether human or animal.

There are two main types of reactions to foods. In one group the reactions are immediate, with symptoms following the ingestion of food within fifteen minutes to an hour. This type gives positive skin reactions. Where the clinical reaction following the ingestion of food is delayed from one to seventy-two hours, positive skin tests are commonly not obtained.

An interesting instance of delayed healing of an abdominal wound due to food

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allergy, probably the first of its kind to be recorded, has been reported by Rowe.⁸⁹ The patient was a thirteen-year-old boy who had had colic in infancy and who for many years had had gastrointestinal symptoms, principally a sore distended abdomen associated with belching, indefinite abdominal distress, cramping pains and other symptoms. Because of these symptoms the appendix was removed at the age of ten and one-half years. The wound did not heal normally, discharging a serosanguinous fluid every two or three weeks. At the age of twelve and one-half years the wound was explored down to the peritoneum. No cause for failure to heal was found, and the discharge persisted.

There was a very definite family history of allergy, and the boy's other symptoms as fatigue, mental dullness, lassitude, and inattentiveness in school suggested allergic toxemia. Skin testing, including tests with various suture materials, was completely negative. The boy was placed on Rowe's fruit and cereal-free elimination diet and the gastrointestinal symptoms disappeared in the course of the second week. The wound also began to heal. This was progressive and complete, and was still healed three years later when the case was reported. By means of the progressive addition of foods to the diet it was found that the difficulty was due to milk allergy.

The theoretical aspects of the problem are thoroughly considered by Rowe who states that an Auer³ type of reaction in the tissues of the wound, or impaired production of collagens and fibroblasts in the tissues of the wound, as suggested by Hopps,⁵⁵ can explain the delayed healing and discharge.

Horesh⁵⁶ states that in gastrointestinal allergy in infants and children inhalant factors have been underemphasized, just as they have been for so many years in chronic atopic eczema in older children. He mentions a case of mucous colitis shown to be due to environmental factors as kapok, feathers and house dust. He also states that allergy must be suspected in children who have an adequate diet, yet fail to gain properly. Irritability due to food allergy in infants and without any other manifestation of allergy is stressed.

The reviewer would like to point out that the term "gastrointestinal allergy" as commonly used refers to two separate and distinct forms of allergy. One form consists of allergic manifestations in the gastrointestinal tract; the other form consists of the manifestations of food allergy, regardless of whether these occur in the gastrointestinal tract or elsewhere. It would clarify considerably discussions in the field of allergy if the term gastrointestinal allergy were restricted to the first form of allergy mentioned, i.e., allergy of the gastrointestinal tract, and the other forms of allergy were discussed as food allergy.

ALLERGY TO VIRUS AND VACCINES

Ratner and Untracht⁷⁹ estimate that at least 1 per cent of the general population is egg-sensitive. It is therefore to be expected that the introduction of virus and rickettsial vaccines grown in chick embryonic tissue and containing components relating to egg-chicken protein will result in allergic reactions in many individuals. Case reports from the literature illustrating this are reviewed.

The authors studied reactions to influenza vaccine A and B in allergic children one to eighteen years of age. Of 108 allergic children, eleven reacted positively on intradermal testing with this vaccine. In every instance, those reacting positively to the vaccine also reacted positively to eggwhite. In no child was there a positive reaction to vaccine and not to eggwhite. This is proof, according to the authors, that the positive reactions to vaccine must be related in large measure or, indeed, entirely to the presence of eggwhite protein in the vaccine.

There are, however, apparently two types of reactions that may ensue from the administration of virus or rickettsial vaccines. The first are the general constitutional reactions characterized by a moderate fever, chills, malaise, and delayed onset of symptoms. Such reactions, though independent of the history of allergy, can vaguely be explained on the basis of reaction to a foreign protein. The second type are the allergic reactions as asthma, urticaria, et cetera. The authors' studies suggest that the second type of reaction is due largely or entirely to the egg protein in the vaccine. They conclude that all persons to whom it is desirable to give the vaccine be first tested intradermally. If the test is negative, then the vaccine may be administered with impunity. If positive, the vaccine may be given provided the usual precautions for administering allergens to which a patient is highly sensitive are observed.

DEATH FOLLOWING VACCINE INJECTION

Deaths related to the injection of foreign protein in man are, according to Werne and Garrow,¹¹⁴ fortunately few. These authors have reviewed the literature on the subject and have reported two cases of their own of extreme interest and impor-

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tance to the pediatrician. They report identical male twins, ten months of age, who died after the second injection of combined diphtheria toxoid and pertussis antigen, alum precipitated. The first injection had been given routinely a month previously from another ampule of the same product. At this time one infant remained symptom free; the other vomited, cried considerably and had a fever of 101° F., but all symptoms subsided uneventfully within a few hours. At the time of the second injection at the age of ten months, no immediate ill effects were noted except that one twin bled slightly from the site of the injection. However, shortly afterwards, both infants vomited, consumed excessive amounts of water, and then "fell asleep," and when next noticed by the parents, they appeared "lifeless." They did not move in bed and could be aroused only by loud noises. One infant had a "staring expression," a temperature of 99° F., and when his diaper was changed, was found to be "ice cold" and "wringing wet with perspiration." Early the following morning, sixteen hours after the injection, one infant appeared dead; the other infant was gravely ill and died four hours later despite heroic efforts at therapy. Complete autopsies were done. Widespread lesions were encountered with vascular injury as the underlying cause. These findings are consistent with death from anaphylactic shock. Postmortem passive transfer tests with the serum of the dead infants and the biological product were negative. Examination of the preparation, which was the product of a very reliable manufacturer, showed sterility and no abnormality, as, for example, excessive free diphtheria toxin. There were no complaints from the use of other batches of the same preparation.

The family history of the infants was negative for allergy except that the father had infrequent attacks of angioneurotic edema. The past history of the infants was essentially negative from every standpoint. The authors answer the question which must be uppermost in the mind of every pediatrician who has read their report, as follows: "In view of the high mortality which accompanies both diphtheria and pertussis during infancy, it is hoped that the publication of these two fatalities will not deter the profession from continuing to practice immunization."

A fatal allergic reaction to influenza vaccine has been reported by Curphey¹⁸. This occurred in a three-and-one-half-year-old girl. There was no family history of allergy. The child had had hives for one day during her first year of life, thought to be due to aspirin. There was no history of sensitivity to egg or chicken. Four hours after the subcutaneous injection of 0.5 c.c. of stock influenza type A and B vaccine, the child developed fever, chills, vomiting, and convulsions. She was hospitalized within two hours after the onset of symptoms but died five hours later, despite all efforts at therapy. At necropsy the whole picture was suggestive of reaction to a foreign protein rather than an allergic reaction in the ordinary sense, since such manifestations as asthma and urticaria were lacking. The author recommends that in the administration of such vaccines an intradermal test should be done with small doses of the antigen, and if local reactions occur, the immunization should be done by the successive injections of small doses at short intervals. This would doubtless protect satisfactorily against the action of the vaccine *per se* as an allergen in the case of children with whom greater precautions must be taken because they react more frequently to egg protein than do adults.

Salk,⁹¹ in commenting upon this report, has made some remarks which in the reviewer's opinion are equally applicable to the cases reported by Werne and Garrow,¹¹⁴ described above. Salk states that toxic reactions to vaccine are proportional in frequency and severity to the concentration of the virus injected. In Curphey's case the findings appear to Salk to be more in accord with a toxic reaction to the virus than to an asymptomatic allergy to some egg constituent in the vaccine. Since the frequency and severity of reactions are related to virus concentration, it would seem reasonable to consider a reduction in the concentration of virus in vaccines for use in children. The dose of virus can be varied over a rather wide range with little influence on mean antibody response in groups given different doses. It might be suggested that caution be exercised in the use of influenza vaccine not only with respect to sensitivity to egg constituents but with respect to the dose of virus given to young children. Until definitive studies are reported, it would seem advisable to reduce the dose for children proportionately more than would be suggested on the basis of size in comparison with the adult.

TREATMENT OF SERUM SICKNESS

The case of a sixteen-year-old boy with severe serum sickness and trismus following the injection of tetanus antitoxin is reported by Appelbaum, Abraham, and Sinton.² The trismus was due to involvement of the temporo-mandibular joints, and many other joints were also involved. He was given one gram of procaine

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hydrochloride dissolved in 500 c.c. of normal saline over a period of two hours. Improvement began before the injection was completed. Another treatment was given on the second day and he was completely symptom-free on the third day. The exact mode of action of procaine in this method of treatment is unknown.

The treatment of serum sickness with Benadryl is reported by Peterson and Bishop.⁷⁴ They report ten cases of serum sickness in children varying in age from two months to eight years. Seven of the children had been treated with horse serum and three with type D anti-Hemophilus influenzae rabbit serum. Repeated oral doses of Benadryl as high as 8 mg. per pound were well tolerated without side reactions even in the youngest infant. Nausea, which was more common with the elixir than with the powder, occurred in several instances but was troublesome in only one case. The authors feel that it may take two or three times as much per pound body weight to control symptoms in infants as compared with adults. In every instance 100 mg. of Benadryl per twenty-four hours completely relieved all manifestations of serum sickness within two or three hours. Of the ten cases treated, nine were completely controlled, and the other was much improved. Adequate therapy was found to consist of from 50 to 100 mg. doses given at six- to eight-hour intervals and continued for the duration of the serum sickness.

DEATH FOLLOWING INJECTION OF TETANUS ANTITOXIN

Gaddner⁸⁵ has reported the case of a fifteen-year-old boy who accidentally cut his finger on a plow. Before the doctor saw the child, he ordered by telephone the administration of 1,000 units of tetanus antitoxin. A small amount of this was injected slowly at first without any untoward reaction and then the remainder was injected. Within ten minutes the boy became nauseated, went into anaphylactic shock, and died an hour after the serum was administered. A complete autopsy was performed. There was no local reaction of any kind at the site of the injection so that it was concluded that the point of the needle must have entered a vein.

PURPURA OF ALLERGIC ORIGIN

Freud and Greenberg⁸³ have reviewed the literature of reactions following the injection of pertussis vaccine, and observed that purpura is rare and has in the past occurred only after repeated injections. They report what is apparently the first case in which the initial injection of pertussis vaccine was followed by generalized purpura. The patient was a one-year-old male Negro infant who was injected with 1 c.c. of the New York City Health Bureau pertussis vaccine (Mishulow). Twenty-four hours later, a bright red petechial rash was noted involving the dorsum of the hands, the extremities and buttocks. Fever was thought to have been present preceding the appearance of the eruption. The child's personal history and family history were negative for allergy, as was his past history. An erythematous indurated area about the size of a penny was noted over the lateral aspect of the left deltoid muscle, the site of the injection. The right forearm, where no injection was given, was edematous with numerous petechiae. The Vollmer patch test and Wasserman reactions were negative. Blood studies were made, the most striking finding being a reduction in platelets.

The child's course was uneventful and he was discharged after ten days. Five months later he was given 0.10 c.c. of the same pertussis vaccine intradermally and a wheal about 1½ inches in diameter with pseudopods appeared at the site of the injection. Seven months later similar tests also resulted in a wheal. Subcutaneous injections of 1 c.c. of the vaccine resulted in local redness and induration, and a rectal temperature of 104° F. Two days later 2 c.c. of the vaccine was injected and this was followed by reddening and induration for twelve hours. None of the intradermal or subcutaneous injections reproduced the purpura which was observed following the initial injection of the vaccine. The authors discussed the reasons for excluding thrombocytopenia as the mechanism for the purpura in this case and believe that the only explanation for the hemorrhagic tendency here appears to be capillary damage due to the liberation of histamine-like substances which are known to increase vascular permeability causing shock and other anaphylactic conditions. They state it is not surprising that the purpura could not be reproduced by repeated injections of the vaccine for rarely does anaphylactoid purpura recur in the same patient. Twenty other children inoculated with pertussis vaccine from the same lot as the patient reported in no instances developed purpura or other anaphylactoid manifestation.

Another case of allergic purpura is described by Donaldson and Scarborough.²² They describe the case of a boy twelve years of age treated with 5 per cent sulfathiazole ointment twice a day because of mild impetigo. Epistaxis and a

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generalized purpuric rash started the evening of the second day of treatment. On the third day the platelets were reduced to 20,000 per c.mm. and capillary resistance was greatly reduced. The other blood changes, except for moderate anemia and prolongation of the bleeding time to thirty minutes, were not remarkable. There was no history of allergy or blood dyscrasia in the boy or his family and he had never previously had sulfonamide therapy. Recovery occurred on discontinuance of the sulfathiazole ointment and daily transfusions for five days. After return of the platelet count and capillary resistance to normal levels, the reapplication of sulfonamides to the intact skin produced striking reduction in capillary resistance at and away from the site of application. Less striking falls in platelet counts were noted. The author considers that these observations point to the importance of the vascular factor (low capillary resistance) as the basis for toxic thrombocytopenic purpura.

ANAPHYLACTOID PURPURA

Sullivan¹⁰⁴ has reported a case with an unusual tendency to bleed which seems best classified as an anaphylactoid purpura. The boy had had two episodes of prolonged bleeding following injury at one and one-half and two and one-half years. During the winters of his sixth and seventh years he had several episodes of warm, red, painful swellings of his ankles. At the age of nine years he was hospitalized for adenotonsillectomy. Blood studies were essentially normal except for moderate anemia and an eosinophilia of 7 per cent. After operation he bled intermittently from the right tonsillar fossa for ten days. A circumcision was done at the same time as the throat operation but this healed without hemorrhage. Further blood studies (bleeding time, venous clotting time, clot retraction time, platelet count, icterus index and tourniquet test) were normal. The boy's condition was critical at times but he recovered after repeated transfusions and such medication as aminoids, amigen, moccasin venom, rutin, ascorbic acid and hykinone. He was discharged after sixteen days but re-admitted three days later because of recurrent right tonsillar fossa bleeding and generalized severe urticaria. This time the bleeding was controlled by one transfusion and the urticaria by Benadryl.

Anaphylactoid purpura (nonthrombocytopenic purpura) is a disease characterized by an abnormal bleeding tendency thought to be due to abnormal or damaged capillaries. The secondary form may occur as a result of acute infections. The diagnosis of primary anaphylactoid purpura should be considered when there is no evidence of infection or intoxication and no abnormalities of the blood can be demonstrated, except occasionally somewhat prolonged bleeding time and frequently a positive tourniquet test. There are two clinical types: (1) Schönlein's purpura in which the joints may become swollen, red and tender, simulating rheumatic fever; petechiae, ecchymoses or urticaria may appear some days later, suggesting the true diagnosis; (2) Henoch's purpura, characterized by abdominal pain, often with vomiting and occasionally with melena; the abdomen is tense and tender; skin lesions occur similar to those of Schönlein's purpura. In both types there is usually fever, leukocytosis and eosinophilia. Treatment is symptomatic. Splenectomy is contraindicated. Toxic substances and allergic factors should be sought. The prognosis is usually good and recovery is spontaneous.

PERIARTERITIS NODOSA

Periarteritis nodosa following scarlet fever in a boy eleven years of age has been reported by Peale, Gildersleeve, and Lucchesi.⁷¹ The vascular lesions were widely distributed about the organs of the body and did not produce gross evidence of nodulation, although numerous petechial and macular hemorrhages were visualized grossly. The patient died of intracerebral hemorrhage and of renal failure. The authors feel that this case lends support to the assumption that periarteritis nodosa may be an allergic manifestation of various causation. In this case the allergic reaction was probably due to the hemolytic streptococci or their products.

Bradley⁷ has described the case of a ten-year-old Filipino boy which resulted in death. The onset occurred about three weeks after an acute sore throat and there was a possible relation to sulfonamide therapy with previous treatments by the same type of drug. The correct diagnosis was suspected during life because of the "telescopic urinary sediment" which appears to be characteristic of this type of vascular disease. This was described by Krupp⁶¹ who states that the urinary sediment in vascular angitis shows simultaneously the changes found in all three stages (Addis classification) of glomerulonephritis. These are red blood cells, white blood cells, red blood cell casts, oval fat bodies, granular casts, hyaline casts,

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and broad casts in a single urinary sediment, accompanied by large amounts of protein.

DRUG ALLERGY

Three cases of penicillin sensitivity have been reported by Sawan²³ in children three, three and one-half and four years of age, respectively. Several findings common to all cases are noted. In all cases the dermal reaction appears between five and ten days after starting the penicillin. The dosage had no relationship to the severity of the subsequent reaction. In no cases was there a personal or family history of allergy or a previous mycotic infection. The reactions consisted of urticaria, severe pruritis, and a mild febrile reaction with other constitutional manifestations. In one case penicillin was continued without aggravation of the urticaria which responded well to Adrenalin and disappeared in forty-eight to seventy-two hours. In the two other cases on discontinuing the penicillin, the manifestations were treated with Benadryl and disappeared within forty-eight hours. Two of the cases were tested intradermally with penicillin and reacted negatively. Two had received previous penicillin therapy during the preceding year. Since all patients were observed within a three-week period and there had been no previous cases, the possibility of an impurity in the penicillin used was suspected but investigation did not substantiate this. Sawan feels that in children skin reactions to penicillin are milder than those of adults and that protean manifestations are less common. He feels that the reactions are not a contraindication for continued use of the drug.

While Dilantin sodium hyperplasia of the gums is not usually thought of as an allergic reaction, the reviewer feels that it should be considered as such since it occurs as a specific reaction to a drug which does not produce this effect in the great majority of patients. Esterberg and White²⁷ report that Dilantin sodium gingival hyperplasia commonly begins at about the age of five years. The incidence then rises sharply from nine to twelve years and then ascends more slowly to a peak at twenty-four years and falls quickly to thirty-five years, after which only scattered cases occur. The initial change consists of a slight inflammation of the interdental papilla, followed by a pinhead tissue extrusion. As a group, these cases showed a remarkably good gingival color. In a few cases where the drug was discontinued, the hyperplasia disappeared, as did excess hair growth which occasionally accompanies the use of this drug. The gingival hyperplasia was found to be independent of the amount or duration of the Dilantin sodium treatment. Local dental conditions, except for the lack of occlusion or brushing, are relatively unimportant in these cases.

Most of the group were dark complexioned; 25 per cent had excess hair; 78 per cent of these showed gingival hyperplasia which occurred in 54 per cent of the entire group. Vitamin C had no effect upon the gingival hyperplasia. No cases of Vincent's angina occurred and no edentulous patients showed hyperplasia. Hyperplasia is predominately in the anterior region on the labial and buccal surface. Brushing and massage greatly tend to retard the hyperplasia. The histological appearance has the general aspect of chronic inflammation. The authors do not mention the presence of eosinophils.

Date¹⁹ has reported two cases of Dilantin sodium hyperplasia of the gums in children which occurred after thirteen and sixteen months of treatment, respectively. No other toxic symptoms, sometimes attributed to Dilantin sodium, appeared in these cases. These symptoms are nystagmus, diplopia, vertigo, ataxia, mental irritability, fatigue, apathy, nausea, vomiting, and occasionally a skin rash. Date states that the overgrowth of the gums is a true hyperplasia which is painless and has no tendency to bleed, thus differentiating it from chronic inflammation of the gums in vitamin C deficiency. The condition tends to disappear if the drug is discontinued.

RHEUMATIC FEVER

One of the most interesting and important diseases of childhood is rheumatic fever. One of the hypotheses as to the etiology of this disease is that it may be an allergic response to hemolytic streptococcus type A of Lancefield or its products. Rittwagen, Romano, and Suigals²⁵ have briefly reviewed the evidence to this effect. Since it is the consensus among allergists that hypersensitivity is usually multiple and that acquired hypersensitivity occurs most frequently in persons with atopy, they investigated the probability of a higher incidence of allergy in children with rheumatic fever as compared to a control of non-rheumatic children. The cases were divided into two groups of 100 children each. One group had proven rheumatic fever. The control group was nonrheumatic. The children ranged in age

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from five to fourteen with an average of ten years. Sixty-four per cent of the rheumatic fever patients either had allergy themselves or had a positive history of allergy in their immediate family, as compared to 18 per cent in the control group. Thirty-three per cent of the rheumatic children had allergies themselves while 31 per cent had parents or siblings with allergy. In the control group only 8 per cent of the children had allergy, and only 10 per cent gave a history of hypersensitivity in their parents or siblings. Thus 65 per cent of the rheumatic fever children gave a positive history of allergy either in themselves or in their immediate families as compared to 18 per cent in the control group. The authors also state that the incidence of hay fever, food allergy, and vasomotor rhinitis is significantly greater in the rheumatic group than in the general population.

MISCELLANEOUS

Schwartz⁹⁴ has re-emphasized the importance of history taking in allergic disease and the favorable position of the pediatrician for noting various incidents related to allergic manifestations. To assist in this he employs a simple ten-year chart blocked off in squares, the abscissa of which indicates the month and the ordinate, the year. The squares are filled in as indicated by various symbols indicating the type of allergic attack or a related manifestation. Such a record will show at a glance in what month the child's symptoms appear, the frequency of attacks, what systems are involved, and the change of shock organ bearing the brunt of the attack. A record of this type is very useful in evaluating the effect of therapy.

In discussing the importance of idiosyncrasies in pediatrics, Clarke¹³ has emphasized the importance of early recognition of one of the most important of these, namely allergy. In early infancy this may take the form of marked dislike for some food to which the child, on careful study, will be found to be allergic. The constantly running nose and recurrent colds so common in this age period are also idiosyncrasies which demand serious consideration from the viewpoint of allergy.

In a general review of allergy in children, Horesh⁹⁵ has listed the various manifestations of allergic disease according to the different body systems. For the purpose of completeness, he includes many conditions suspected but not proven to be allergic in nature.

Pennington⁷² has also published a general review of allergic conditions in infants and children. She draws attention to the fact that some of the difficulty in breathing formerly attributed to an enlarged thymus may be an allergic difficulty. In fact many of the deaths diagnosed as thymic are possibly allergic in origin. Frequent recurrence of croup should always lead one to suspect an allergic disease. The importance of careful history taking is also stressed. Skin tests are rarely necessary before the age of six months because of the relatively limited number of allergens to which the child is exposed. Orange juice may be replaced for a trial period by lemon or tomato juice or by ascorbic acid. (The reviewer's experience is that if one citrus fruit disagrees, others will also). The prophylaxis of allergic disease is stressed. She emphasizes that in the care of allergic infants and children, only one food at a time should be added and it should be given slowly and in gradually increasing amounts. Children with glandular deficiencies are often improved by the addition of specific therapy when possible.

Clark and Rosenberg¹¹ have described the case of a four-year-old colored boy hospitalized because of atonic seizures involving the upper extremities. He had had a similar seizure three months previously. There was no family or personal history of allergy. Physical findings, including the neurological, were not remarkable. Blood eosinophilia varied between 4 and 12 per cent. On stool examination the ova of *Ascaris lumbricoides* and *Trichuris trichuria* were found. The skin test for *Ascaris* was positive. X-rays of the chest were taken on seven different occasions and showed the typical migrating lesions of Loeffler's syndrome. Anthelmintic therapy was administered; the patient's temperature remained practically normal during his course in the hospital, which was practically asymptomatic, and he was discharged as improved after about four weeks. The authors point out that this case with its transient pulmonary infiltrations, eosinophilia, mild clinical course, and variable x-ray findings, fleeting and migratory, out of proportion to the mild signs and symptoms is characteristic of Loeffler's syndrome. This condition is splendidly reviewed. From this review the authors conclude that Loeffler's syndrome is an allergic phenomenon, usually occurring in individuals with allergic tendencies as the result of various allergens. The condition appears to represent an eosinophilic pneumonitis in which the interstitial tissue of the lung is the shock organ. There is no specific treatment other than the removal of the offending allergen when possible, and spontaneous recovery commonly occurs without complications. Of particular

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importance to the pediatrician is the fact that Swiss observers have emphasized the rather frequent association of the syndrome with *Ascaris* infestation.

Heinild and Madsen⁵⁰ tested 140 children two to fourteen years of age with an extract of pin worms (*Enterobius vermicularis*). The children reacted in a non-specific manner, and no diagnostic value could be attached to this test.

In a previous review,^{43c} a skin test devised by Leftwich⁶² for determining sensitivity to sulfonamides was described. Fink, Furton and Wheeler²⁹ checked this test by studying nineteen children under twelve years of age who had previously developed fever upon the administration of sulfadiazine or sulfathiazole, nine of whom developed immediate fever and rash upon subsequent oral administration of the offending sulfonamide. All tests were negative and the authors conclude that skin testing for sulfonamide sensitivity by the method of Leftwich using intradermal injections of serum from patients receiving sulfonamide medication is not applicable to children.

Gaál³⁴ has reported a case of paroxysmal tachycardia in an infant. This was a full-term baby who was breast fed to the age of three months. Eczema had developed at the age of two and one-half months. The parents stated at times that the child would breathe very noisily. At the age of six months he developed an upper respiratory infection which was followed in a few days by severe dyspnea. He was hospitalized and found to have a generalized dry eczema. The breathing was asthmatic with audible respirations. The lungs were hyper-resonant and the diaphragm depressed. The heart sounded like the ticking of a watch. The rate was 220. The liver edge extended down to the umbilicus and the spleen two fingers below the costal margin. An electrocardiogram showed auricular tachycardia of ventricular origin.

Following the administration of various medications the asthma ceased but the tachycardia persisted. On the third day, following a large dose of digitalis and "Corhormon," the cardiac rate fell to 112 and the liver and spleen receded. The following day the child developed a right hemiplegia believed to be due to an embolus. A few days later the asthmatic breathing recurred but responded to epinephrine. The child gradually improved and was discharged from the hospital, and six months later was reported in normal health, the paralysis having disappeared. Gaál feels that the tachycardia was probably due to a focus of mild carditis set up by the infection preceding the asthmatic attack.

Horesh⁵⁸ briefly reports a case of sighing dyspnea in a thirteen-year-old girl. Her brother had asthma and the mother was certain that the child was also developing asthma. This child had the uncontrollable desire to fill her lungs with air at five or ten-minute intervals, taking deep breaths, and complaining that she had difficulty in taking them. The case was not discussed further.

Allergic toxemia, according to Horesh,⁵⁶ is a definite symptom complex in children. This is easily recognized if one keeps it in mind as it is usually seasonal and frequently due to pollen. These children show none of the usual signs of hay fever, but they may have indefinite signs of nasal allergy which are discovered only by examination. The chief complaint is fatigue, loss of ambition, dullness, listlessness, mental sluggishness, and somnolence. One mother complained that she would frequently find her three-year-old child, who had been playing in the living room, fast asleep. This was quite a shocking experience to a parent who had been accustomed to believe that her child was always full of energy and could never sit still. In Horesh's experience these children give strong positive reactions to pollens and they sooner or later develop frank hay fever.

Horesh also emphasizes the fact described by Hooker⁵⁴ that there is a difference between breeds of dogs and dog dander sensitivity and it may be necessary to test with the dander of the patient's own dog. The reviewer feels that this fact has important connotations. If it is true of dogs, there is no reason to suppose why it should not be true of all other fur-bearing animals. This renders the diagnosis of sensitivity by skin tests much more difficult. The reviewer feels that the general principle of avoidance of epidermoids by allergic individuals, regardless of skin tests, is an important prophylactic and therapeutic measure.

The treatment of pediculus capitis in school children with DDT powder has been described by Kaiser.⁶⁰ The powder is used in a 10 per cent mixture with inert talc. This is sprayed on the child's hair, the application being repeated at the end of one week and sometimes again a week later. Three hundred and fifty children were treated with complete success without harm of any kind. The reviewer feels that the fact that contact dermatitis did not result from the use of this powder is very important because of the present widespread use of DDT. However, this series is relatively small, and the pediatrician must be alert to the possibility of allergic reactions to DDT.

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The review of the literature of asthma by Unger¹⁰⁰ and the questionnaire published by Mulligan⁹⁹ contain much of interest to the pediatric allergist but do not readily lend themselves to abstracting. A new journal, the *Quarterly Review of Allergy and Applied Immunology*,* under the editorship of Dr. Fred W. Wittich, contains many abstracts of interest to the pediatric allergist.

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CONVULSIONS FOLLOWING EPINEPHRINE

(Continued from Page 153)

SUMMARY

A case history is presented of a patient who had convulsive seizures after the use of epinephrine which was probably due to hyperventilation tetany produced by the stimulating effect of this drug on his central nervous system.

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★ *In Memoriam* ★

IRVING SYDMORE BARKSDALE

We exceedingly regret to announce the death of Dr. Irving Sydmore Barksdale, 610 Crescent Avenue, Greenville, South Carolina.

Doctor Barksdale was an Active Fellow of the College. He was born in Richmond, Virginia, December 28, 1897. He attended McGuire University School, a private school for boys in Richmond, where he prepared for College. He entered the University of Richmond for his pre-medical course, which was interrupted by his enlistment with the Richmond Blues, with which he saw service on the Mexican Border. He also served overseas in France and was discharged in 1919 to resume his medical studies at the Medical College of Virginia. He finished his medical work at Yale in 1923. He taught Physiology at the Medical College of South Carolina and then spent seventeen years as Commissioner of Public Health in Greenville. While he held this position, he became interested in allergy under the influence and guidance of the late Dr. Warren T. Vaughan.

In his spare time he devoted himself to research, and the Table Rock Laboratories of Greenville were established through his research efforts. Their first two products of manufacture, Citrin, a blood pressure lowering medicine made from the active principle of watermelon seed, and Bismuth Violet, an antibiotic, were his original contributions.

Doctor Barksdale was vice president of the Table Rock Laboratories at the time of his death. He was a Fellow of the American Public Health Association and of the American Medical Association. Doctor Barksdale was secretary of the Greenville County Medical Society for the years 1926, 1927, 1928, 1929, and 1930, and he was president of the Society for the year 1931. He was a member of the Southern Medical Association, Tri-State Medical Association of Virginia, and the Medical Societies of North and South Carolina.

Doctor Barksdale was a staff member of the Greenville General Hospital and St. Francis Xavier Hospital of Greenville. For the past three and one-half years he was in private practice. He had published twenty-three articles, including a wide scope of subjects on public health, pharmacology, bacteriology, and allergy.

Doctor Barksdale is survived by his wife, Laurette; his son, George; his daughter, Elizabeth; his parents, Dr. and Mrs. George E. Barksdale, of Richmond, Virginia, and two sisters, Mrs. Marshall Roberts of Louisville, Kentucky, and Mrs. Thomas Alexander of Waynesville, North Carolina.

Members of the College extend their sincere sympathy to the family.

F.W.W.

The new 1948 Catalogue of Timely Medical Books, published by Grune & Stratton, Inc., 381 Fourth Avenue, New York 16, New York, has made its appearance. It is a résumé of publication dates of 109 books. It also lists the fifteen periodicals published and distributed by Grune & Stratton. These timely books cover latest developments in medicine and surgery and the other various specialties.

News Items

THE FOURTH ANNUAL MEETING

The fourth annual meeting of the American College of Allergists was held March 12, 13, and 14, 1948, at the Hotel Pennsylvania, New York, New York. The attendance exceeded that of all previous meetings, with a registration of 550. The success of this meeting must be credited to Dr. Harold A. Abramson, chairman of the Program Committee, with the hearty co-operation of the other members of his committee, Drs. Robert F. Hughes, John H. Mitchell, Homer E. Prince, Bret Ratner, Harry L. Rogers, and George L. Waldbott, as well as to Dr. M. Murray Peshkin, chairman of the Committee on Local Arrangements and his Host Committee which consisted of members of the College in the metropolitan area. This Host Committee contributed most generously toward defraying the expenses of the cocktail hour, the flowers, and the music.

No formal or informal exhibits were displayed at this meeting. Sessions were devoted entirely to a scientific program.

The following program was presented:

Friday, March 12

Morning Session—9:30 A. M.

Chairman: M. MURRAY PESHKIN, M.D., New York, New York

Sensitivity to Petrolatum and Ointment Bases

SAMUEL J. LEVIN, M.D., and SELMA S. MOSS, M.D., Detroit, Michigan.

Clinical Evaluation of a New Antihistaminic Drug—Antistine

MORRIS A. KAPLAN, M.D., and NORMAN J. EHRLICH, M.D., Chicago, Illinois.

Effect of Substitution of Antistine for Benadryl or Pryribenzamine During the Height of the Ragweed Pollen Season

BERNARD DICKSTEIN, M.D., Flint, Michigan.

A New Antihistaminic Compound, Histadyl for the Treatment of Urticaria and Hay Fever

SALVATORE SALETTA, M.D., Chicago, Illinois.

Correlation of Experimental Data with Clinical Behavior to Synthetic Antihistaminic Drugs

ALEX S. FRIEDLAENDER, M.D. and SIDNEY FRIEDLAENDER, M.D., Detroit, Michigan.

The Clinical Evaluation of a New Histamine Antagonist, "Decapryn"

ETHAN A. BROWN, M.D., ROBERT WEISS, M.D., and JOSEPH P. MAHER, M.D., Boston, Massachusetts.

Histamine-Sympathin Balance

FRANCISCO J. FARRERONS-CO, M.D., Barcelona, Spain.

Antitoxic Immunity Induced by Booster Dose of a Refined Diphtherial Toxoid in Allergic Children

H. G. RAPAPORT, M.D., and M. MURRAY PESHKIN, M.D., New York, New York.

Afternoon Session—2:00 P. M.

Chairman: BRET RATNER, M.D., New York, New York

The RH Factor in Immunological Reactions

ALEXANDER S. WIENER, M.D., Brooklyn, New York.

Immediate Urticarial Reactions to Intradermal Injections of Bacterial Antigens

BENNETT KRAFT, M.D., MARK H. MOTHERSILL, M.D., and R. H. NESTMAN, M.D., Indianapolis, Indiana.

Sinusitis Allergy and Bacterial Vaccine

K. A. BAIRD, M.D., West St. John, N. B., Canada.

Evaluation of the Patch Test Based on Experimental Findings

MAX GROLNICK, M.D., Brooklyn, New York.

***Repeated Patch Testing in Allergic Eczematous Sensitization**

VICTOR H. WITTEN, M.D., and HILLIARD M. SHAIR, M.D., New York, New York.

NEWS ITEMS

***Skin Tests with Endocrine Substances**

(Method of Zondek and Bromberg.)

RODOLF L. BAER, M.D., VICTOR H. WITTEN, M.D., and JAMES R. ALLEN, M.D.,
New York, New York.

Common Surgical Problems Which Often Masquerade As Asthma

RICHARD H. OVERHOLT, M.D., Boston, Massachusetts.

Saturday, March 13

Morning Session—9:00 A. M.

Chairman: GEORGE E. ROCKWELL, M.D., Milford, Ohio

Anaphylactic Shock in Mice Induced by a Traceable Colored Antigen

PHILIP D. MCMASTER, M.D., New York, New York.

Patterns of Allergic Sensitization

ROGER P. WODEHOUSE, Ph.D., Pearl River, New York.

Pruritus Vulvae Associated with Hay Fever

WILLIAM F. MITCHELL, M.D., Columbus, Ohio.

Inhalation Therapy—Demonstration of Improved Methods

STEPHEN D. LOCKEY, M.D., Lancaster, Pennsylvania.

Clinical Experience and Experimental Studies with Isuprel in Bronchial Asthma

IRVING W. SCHILLER, M.D., FRANCIS C. LOWELL, M.D., and JOHN CURRY, M.D.,
Boston, Massachusetts.

Weather and the Asthmatic State

Special reference to the Course of Asthma during September, 1947, in the District
of Columbia.

HARRY S. BERNTON, M.D., and ARNOLD S. GREENBERG, M.D., Washington, D. C.

Allergy in Cuba

G. ESTRADA DE LA RIVA, M.D., Havana Cuba.

Afternoon Session—2:00 P. M.

Chairman: HAL M. DAVISON, M.D., Atlanta, Georgia

Clinical Significance of Acetylcholine

JOSEPH GARDNER HOPKINS, M.D., New York, New York.

Transmission of Nervous Impulse

OTTO LOEWI, M.D., New York, New York. Nobel Laureate in Medicine, 1936.

Comparison of Antihistaminic Action of Pyribenzamine and Epinephrine in the

Human Skin by Electrophoresis

HAROLD A. ABRAMSON, M.D., New York, New York, and SAMUEL GROSBERG,
M.D., Boston, Massachusetts.

The Separation of Antibody-Antigen Reaction from Response of Smooth

Muscle by Ammonium Salts

A. J. WEIL, Ph.D., and EDNA ROSE, New York, New York.

4:00 P. M. **Business Meeting**

6:00 P. M. **Cocktail Hour**

New York Metropolitan Committee—Host.

7:30 P. M. **Informal Banquet**

Sunday, March 14

Morning Session—9:00 A. M.

Chairman: BAYARD T. HORTON, M.D., Rochester, Minnesota

Bacteriologic Studies in Multiple Sclerosis

EDWARD C. ROSENOW, M.D., Cincinnati, Ohio, and BAYARD T. HORTON, M.D.,
Rochester, Minnesota.

Studies in Acute Disseminated Encephalomyelitis in Rhesus Monkeys

ELVIN M. KABAT, Ph.D., ABNER WOLFF, M.D., and ADA E. BEZER, New York,
New York.

Retrobulbar Neuritis: Treatment with Histamine

HENRY P. WAGENER, M.D., and BAYARD T. HORTON, M.D., Rochester, Minnesota.

Electroencephalogram of Allergic Children

SUSAN C. DEES, M.D., and HANS LOWENBACH, M.D., Durham, North Carolina.

**Paper deals with work done under the Lucier Grant for Dermatologic Allergy during the past
two years.*

NEWS ITEMS

Afternoon Session—2:00 P. M.

PANEL DISCUSSION

Chairman: HARRY L. ROGERS, M.D., Philadelphia, Pennsylvania

Otolaryngologic Phases of Allergy

FRENCH K. HANSEL, M.D., St. Louis, Missouri.
KENNETH K. CRAFT, M.D., Indianapolis, Indiana.
JEROME GLASER, M.D., Rochester, New York.
IRVING B. GOLDMAN, M.D., New York, New York.
M. MARTYN KAFKA, M.D., New York, New York.
GRANVILLE F. KNIGHT, M.D., White Plains, New York.
HUGH A. KUHN, M.D., Hammond, Indiana.
JOHN H. MITCHELL, M.D., Columbus, Ohio.
WALTER E. OWEN, M.D., Peoria, Illinois.

PANEL - AT - LARGE

Members and Guests of the College.

PAPERS PRESENTED BY TITLE

Standardization Procedures for Determination of Aerosol Delivery of Nebulizers by Phenolsulfonphthalein Aerosols

HAROLD A. ABRAMSON, M.D., CARL REITER, M.D., BERNARD SKLAROFKY, A.B., and HENRIETTE H. GETTNER, M.S., New York, New York.

The Use of Oral Potassium Iodide in Atopic Dermatitis

ETHAN ALLAN BROWN, M.D., Boston, Massachusetts.

A Study of One Hundred Allergic Individuals by the Minnesota Multiphasic Personality Inventory Test

ETHAN ALLEN BROWN, M.D., I. ALAN ANNIS, M.D., and LIONEL P. GOITEIN, M.D., Boston, Massachusetts.

An Evaluation of Routine X-Ray Studies in Asthmatic Patients

ETHAN ALLAN BROWN, M.D., MAX RITVO, M.D., and MEYER RITVO, M.D., Boston, Massachusetts.

Behavior of the Normal Histamine of the Rabbit Toward Anti-Histaminic Substances

FRANCISCO J. FARRERONS, M.D., Barcelona, Spain.

Aerosol Penicillin in Allergic Patients with Respiratory Infections

MAYER A. GREEN, M.D., Pittsburgh, Pennsylvania.

Coccidioidomycosis Treatment with Histamine

HINTON D. JONEZ, M.D., Tacoma, Washington.

Multiple Sclerosis, Histamine and Curare

HINTON D. JONEZ, M.D., Tacoma, Washington.

The Diagnosis and Treatment of Perennial Allergic Rhinitis

A. L. MAIETTA, M.D., Boston, Massachusetts.

Respiratory Allergy—an Analysis of Subjective and Objective Symptoms Observed Under Test Conditions

HERBERT J. RINKEL, M.D., Kansas City, Missouri, and JACQUES M. SCLAFFER, Paris, France.

Unexplained Fever

ALBERT H. ROWE, M.D., Oakland, California.

Massive Spontaneous Subcutaneous Emphysema Occurring in an Asthmatic Attack

MAURY D. SANGER, M.D., New York, New York.

Evaluation of Therapeutic Substances Employed for the Relief of Bronchospasm

MAURICE S. SEGAL, M.D., JOHN F. BEAKEY, M.D., ELLIOTT BRESNICK, M.D., and LEON LEVINSON, M.D., Boston, Massachusetts.

Whale Oil, Trichophytin and Autoserotherapy in the Treatment of Epidermophytosis

PERRY SPERBER, M.D., Providence, Rhode Island.

Twelve Years Experience with Fungi

CARL P. WAGONER, M.D., Vancouver, B. C., Canada.

Chronic Urticaria—an Etiological Survey

GEORGE L. WALDBOTT, M.D., and CHARLES SPRINKLE, M.D., Detroit, Michigan.

NEWS ITEMS

An Adapter for the Rapid Performance of the Puncture Skin Test

A. I. KLEINMAN, M.D., Brooklyn, New York.

Industrial Dermatitis Control

NATHAN FRANCIS, M.D., Rochester, New York.

Non-Reagin Allergy

M. G. MEYER, M.D., Michigan City, Indiana.

Registration commenced Thursday, March 11, at 2 p. m., under the auspices of a very efficient corps of three registrars furnished complimentary by the New York Convention Bureau. Through their services the large registration was handled very smoothly. The banquet was the largest attended in the history of the College and was highlighted by a dinner dance. The wine for the banquet was generously supplied by the Nepera Company, Yonkers, New York.

At the business session of the Board of Regents, Thursday, March 11, it was decided that the next annual meeting of the College will be held at the Palmer House, Chicago, Illinois, April 14, 15, 16, and 17, 1949. The scientific sessions will be held in the Red Lacquer Room of the Palmer House April 15, 16, and 17. There will be large industrial and scientific exhibits, extending from noon April 14 to noon April 17. Registration commences April 14, at 2 p. m.

The Board of Regents also voted that the Fall Postgraduate Instructional Course in Allergy in 1949 will be held the first week in November at Baylor University, Houston, Texas.

At the business meeting of the Board, fourteen members were elevated to Active Fellowship. The College now has almost 800 members.

During the past year the College has been unfortunate in the loss, through death, of the following: Dr. Charles W. Karraker, Louisville, Kentucky, and Dr. Philipp Schonwald, Seattle, Washington. Obituaries have appeared in the *ANNALS OF ALLERGY* and condolences have been sent to the families.

At the general business meeting of the College, Saturday, March 13, the following officers were elected to serve for one-year terms: President-Elect, Dr. Jonathan Forman, Columbus, Ohio; First Vice-President, Dr. Jerome Glaser, Rochester, New York; Second Vice-President, Dr. Edward Tatge, Evanston, Illinois. Dr. George E. Rockwell of Milford, Ohio, was elected by ballot in 1947 and became President, succeeding Dr. Hal M. Davison. The following members were elected to serve on the Board of Regents for two-year terms: Dr. W. Byron Black, Kansas City, Missouri; Dr. G. Estrada de la Riva, Vedado, Havana, Cuba; Dr. Robert F. Hughes, Hamilton, Ontario, Canada; Dr. Katharine MacInnis, Columbia, South Carolina; and Dr. Boen Swinny, San Antonio, Texas. Those remaining on the Board of Regents until 1950 are: Dr. Harold A. Abramson, New York, New York; Dr. Jonathan Forman, Columbus, Ohio; Dr. John H. Mitchell, Columbus, Ohio, and Dr. Albert V. Stoesser, Minneapolis, Minnesota. Dr. George E. Rockwell, President of the College, is the tenth member of the Board of Regents, according to the amended By-Laws.

A detailed report on the College finances was read by the Secretary, as prepared by the Certified Public Accountant, and was approved. A financial report on the *ANNALS OF ALLERGY* was included.

Dr. M. Murray Peshkin reported on the progress made on autonomous certification in allergy. He presented the joint resolutions adopted by the College and the Academy when appearing before the chairman of the Advisory Committee on Medical Specialties (See January-February issues of the *ANNALS*). Doctor Peshkin reported that Doctor Kirklin, chairman of the Committee on Medical Education and Hospitals, has subsequently notified this joint committee that action on the joint resolutions has been deferred.

NEWS ITEMS

The following change in the By-Laws was unanimously approved at the general business meeting:

"ARTICLE V. Board of Regents. *Section 1. Membership.*—There shall be a Board of Regents of the College. The Board shall consist of the President; the Secretary-Treasurer who shall be an ex-officio member; together with nine (9) additional members who shall be elected from and by the Fellows of the College. The first Board of Regents shall be elected at such time and place as the first Board of Directors may determine. Three of said first Board of Regents shall be elected to serve for a one-year term, three shall be elected to serve for a two-year term, and three shall be elected to serve a three-year term. Thereafter, and annually, Regents shall be elected to serve for three-year terms.

"If an elective Regent shall during his term of office become either the President or Secretary-Treasurer of the College, the Board of Regents shall thereafter at once declare that a vacancy exists in his elective place on the Board and proceed to fill the vacancy in the manner prescribed in Section 2 of this article.

"Section 4. Chairman. The President shall preside at all meetings of the Board of Regents and shall execute all duties delegated to him by the Board. In case of the absence of the President at any meeting, the Board may designate one of its number to preside at such meeting."

It was decided at the business meeting of the Board that the officers would retire at the expiration of each annual session rather than the first of June, since the annual meetings are now held in the early spring. The newly elected officers took charge immediately.

The business session adjourned with the introduction of the new President, Dr. George E. Rockwell.

AMERICAN BOARD OF ALLERGY

The secretaries of all sectional and regional societies have been asked to bring before their societies a motion to pass a resolution in favor of an American Board of Allergy. Most of the secretaries of these societies have asked that a postal card vote be taken of their individual members so that they may have a record for their files. This would serve as a mail vote to decide the matter, providing the society is not meeting before the Combined Committee on Certification of the American Academy of Allergy and the American College of Allergists meets with the AMA committees interested. A printed postal card has been sent to all societies to obtain this vote from their respective members. This does not in any way conflict with the postal card vote taken among the practicing allergists in the United States with regard to the matter of certification by the Combined Committee of the Academy and the College.

AMERICAN SOCIETY OF OPHTHALMOLOGIC AND OTOLARYNGOLOGIC ALLERGY

The American Society of Ophthalmologic and Otolaryngologic Allergy will hold its regular annual meeting at the Palmer House, Chicago, Illinois, October 8 and 9, 1948. An excellent program covering all phases of allergy has been prepared. Dr. W. Byron Black, 530-535 Professional Building, Kansas City, Missouri, is President, and Dr. Francis L. McGannon, 14900 Detroit Avenue, Lakewood 7, Ohio, is Secretary-Treasurer. There will be a round-table discussion, business meeting, luncheon, cocktail hour, and banquet. All the members are urged to attend.

CANADIAN SOCIETY FOR THE STUDY OF ALLERGY

The Canadian Society for the Study of Allergy will meet in Toronto on June 22, 1948, at the Royal York Hotel. Dr. Isaac H. Erb, F.A.C.A., 8 Burnside Drive, Toronto 10, Ontario, Canada, is the President, and Dr. John R. Ross, 262 St. Clair Avenue West, Toronto 12, Ontario, Canada, is the Secretary. A cordial invitation has been extended to all members of the College to attend.